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Reports of myocarditis and pericarditis following mRNA COVID-19 vaccines: A systematic review of spontaneously reported data from the UK, Europe, and the US and of the literature

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Abstract

Objectives: To bring together spontaneously reported data from multiple countries to estimate reporting rate, and better understand risk factors for myocarditis and pericarditis following COVID-19 mRNA vaccines.

Design: Systematic review of spontaneously reported data from United Kingdom (UK), United States (US), and European Union/European Economic Area (EU/EEA) and of the literature.

Data sources: UK Yellow Card scheme, Vaccine Adverse Event Reporting System (VAERS), EudraVigilance were searched from date of vaccine launch to 21 October 2021. PubMed and Embase were searched to 11 October 2021.

Eligibility criteria: We included publicly available spontaneous reporting data for "Myocarditis" and "Pericarditis" from UK, US, and EU/EEA following COVID-19 mRNA vaccines. Pharmacoepidemiological observational studies investigating myocarditis/pericarditis following mRNA COVID-19 vaccines were included (no restrictions on language or date). Critical Appraisal Skills Programme (CASP) tools assessed study quality.

Data extraction and synthesis: One researcher extracted data. Spontaneously reported events of myocarditis and pericarditis were presented for each data source, stratified by vaccine, age, sex, and dose (where available). Reporting rates were calculated for myocarditis and pericarditis for each population. For published pharmacoepidemiological studies, design, participant characteristics, and study results were tabulated.

Results: Overall, 5295 reports of myocarditis and 3453 reports of pericarditis had been submitted to the UK, US, and EU/EEA regulators during the study period. Most reports (73.3%) followed Comirnaty (Pfizer/BioNTech). Males represented 74.9% and 56.9% of myocarditis and pericarditis reports, respectively. Most reports concerned vaccinees aged <40 and were more frequent following a second dose. Reporting rates were consistent between the data sources. Seven pharmacoepidemiological studies were included; results were consistent with our spontaneous report analyses.

Conclusions: Younger vaccinees more frequently report myocarditis and pericarditis following mRNA COVID-19 vaccines than older vaccinees. Most cases had mild clinical course followed by full recovery. Results from published literature supported the results of our analyses.

Strengths and Limitations of the Study

- This is the first study to bring together spontaneously reported data from the United Kingdom, United States, and Europe on myocarditis and pericarditis following mRNA COVID-19 vaccines.
- Results from this study provide evidence on the frequency of reported events of myocarditis and pericarditis following mRNA vaccines in different age groups, and by sex and vaccine dose. Analyses of spontaneous reports were consolidated with results of published literature, identified by systematic review.

- Results may have been influenced by biases including different vaccination policies in each region examined, and publicity on events of myocarditis and pericarditis following mRNA vaccines.
- The study relied on outputs from spontaneous reporting systems in which the level of detail differed between the systems examined; furthermore, it is not possible to estimate incidence rates using spontaneous reports due to the lack of data on the exposed population, and there is no unvaccinated comparison group.
- There is an urgent need for further pharmacoepidemiological studies to be conducted to provide more accurate estimates of the frequency, clinical course, long term outcome, effects of treatment and impact on quality of life, to address many of the limitations of spontaneous reporting.

1.0 Introduction

Myocarditis and pericarditis (inflammation of the heart muscle and inflammation of the sac that surrounds the heart, respectively) have recently been recognised as very rare adverse effects of messenger RNA (mRNA) vaccines against coronavirus disease 2019 (COVID-19), manufactured by Pfizer/BioNTech and Moderna (1-4). In the general population, myocarditis is diagnosed in approximately ten to 20 individuals per 100,000 per year, and has been demonstrated as more commonly diagnosed in males and in younger age groups (mostly in vaccinees aged under 40 years) (5). In the general population of the United Kingdom (UK) in 2020, the rate of myocarditis was 11.05 (9.74-12.48) cases per 100,000 person-years (6). Symptoms indicative of myocarditis or pericarditis after COVID-19 vaccine include: new onset and persisting chest pain, shortness of breath, or palpitations following vaccination (7). The United States' (US) Centers for Disease Control and Prevention (CDC) advise that medical attention is sought if symptom onset is within one week of receiving an mRNA vaccine (1). Where possible, suspected cases should be evaluated, provided guidance, and be followed up with a cardiologist [3]. It is important that differential diagnoses, including COVID-19 infection, are considered and ruled out (7).

The signal of myocarditis and pericarditis following mRNA vaccines was first identified in Israel in May 2021, where there had been 148 cases of myocarditis reported within 30 days of vaccination, with the majority of these cases (n=121) reported after the second dose (4). At this time, Israel had rapidly rolled out the Pfizer/BioNTech mRNA COVID-19 vaccine (Comirnaty) to its population and was amongst the first countries to provide widespread COVID-19 vaccines to young adults (4, 8). The Israeli Ministry of Health appointed an epidemiological team to investigate the possible link between these cases of myocarditis and the vaccine (4). Results from this assessment were that there was a possible link between the second vaccine dose and the onset of myocarditis among young men aged 16 to 30 (4). This link was found to be stronger amongst 16-19 year olds compared with other age groups (4).

After the signal initially emerged in Israel, further cases of myocarditis and pericarditis following mRNA COVID-19 vaccines were reported in multiple countries (7). The World Health Organisation's (WHO) Global Advisory Committee on Vaccine Safety (GACVS) issued a statement on 9 July 2021, outlining the emerging signal of myocarditis and pericarditis (7). On 19 July 2021, a Dear Healthcare Provider letter was issued by the European Medicines Agency, to bring clinicians' attention to this possible adverse event of vaccination (2). Furthermore, the product information for both mRNA vaccines was updated to include myocarditis and pericarditis as an adverse event of unknown frequency in the UK, Europe, and the US (9-15). Data suggest that the immediate course of myocarditis and pericarditis following vaccination is generally mild and responds to treatment such as rest, and nonsteroidal anti-inflammatory medications (7). In Israel it was determined that vaccinees who develop myocarditis or pericarditis often require short-term hospitalisation (4). Although most cases appear to have mild severity, further follow-up of cases is ongoing to determine the long term outcomes of myocarditis and pericarditis following mRNA vaccines (1, 7).

As vaccine policies in the UK, US, and EEA progress into their advanced stages, the focus has shifted towards vaccinating adolescents and young adults, with both Pfizer/BioNTech and Moderna vaccines (Comirnaty and Spikevax, respectively) authorised for use in

children over the age of 12 years in each of these regions (with the exception of Spikevax in the US) (10-15). In the UK, all children and adolescents aged 12 to 17 years have been offered a first dose of COVID-19 vaccine (16). For those who are clinically extremely vulnerable, live with somebody who is clinically extremely vulnerable, or turn 18 years of age in the following three months, a second dose is offered (16, 17). In the EU, Comirnaty was initially approved for use in children and adolescents aged 12 and over in May 2021 and Spikevax was authorised for this age group in July 2021 (18). As of November 2021, both mRNA vaccines are under review to extend their use for children aged five years and older (19, 20). Meanwhile in the US, Comirnaty has been approved for use in children aged five and over (21).

From the data available, young men and adolescent males appear at higher risk of myocarditis or pericarditis following exposure to mRNA vaccines, with cases occurring within a few days of vaccination (7). The event appears to occur more frequently following the second dose of the vaccine. Individual regulatory authorities continue to monitor the events of myocarditis and pericarditis in their own spontaneous reporting systems (2, 3, 22). The clinical course is typically mild and self-limiting, with most cases making a full recovery (23). While the majority of vaccinees experiencing myocarditis or pericarditis after mRNA vaccination are below the age of 40, older patients have also developed these events. It is currently not known at what frequency myocarditis and pericarditis may occur following a third dose of COVID-19 vaccine. Due to the characteristics of the population offered a third dose at present (clinically extremely vulnerable), it is likely that increasing numbers of vaccinees offered a third dose will have pre-existing health conditions. These people were vaccinated early in the programme, and thus are likely to have received an adenovirus vector vaccine for their first two doses. Vaccinees receiving a third dose of COVID-19 vaccine need to be monitored intensively to determine the frequency and severity of myocarditis and pericarditis following mRNA COVID-19 vaccines, and to identify any newly emerging safety concerns.

We aimed to bring together spontaneously reported data from several countries to better understand risk factors for myocarditis and pericarditis following exposure to COVID-19 mRNA vaccines. This is important because young adults are or will be receiving mRNA COVID-19 vaccinations in the UK and EU. Also, only mRNA vaccines have been authorised for use in children older than 12 years. Third doses of COVID-19 vaccines have also begun to be administered. The results from this study will inform risk of myocarditis and pericarditis following mRNA vaccines in each subpopulation.

2.0 Materials and Methods

Spontaneous reporting outputs of the UK (Yellow Card scheme), US (Vaccine Adverse Event Reporting System [VAERS] via the CDC Wonder online tool), and European Economic Area ([EEA] EudraVigilance) were used to estimate the frequency of reported cases of myocarditis and pericarditis following COVID-19 Vaccine Pfizer/BioNTech (Comirnaty) and COVID-19 Vaccine Moderna (Spikevax) (24-26). All cases of myocarditis and pericarditis which had been spontaneously reported to these systems between the date of vaccine launch and the datalock point were counted. Cases were stratified by age, sex, and vaccine dose where these data were available.

Data on events labelled “Myocarditis” and “Pericarditis” were obtained from each database. The datalock point was 21 October 2021 for VAERS and EudraVigilance, and 20

October 2021 for the Yellow Card scheme. Data from the Yellow Card scheme is released weekly, with data up to 20 October 2021 the closest release to the 21 October 2021 datalock point used for VAERS and EudraVigilance.

The number of vaccinated individuals per vaccine brand in the UK, US, and EEA were obtained from the websites of the MHRA, the CDC in the US, and the European Centre for Disease Prevention and Control (ECDC) up to the date closest to the datalock point for ADR spontaneous reports (3, 27, 28). Reporting rates of myocarditis and pericarditis per million vaccines administered were calculated for those who had received at least one dose of each vaccine brand.

2.1 Literature Review

A systematic literature review was conducted using PubMed/Medline and Embase literature databases. No review protocol was prepared.

The datalock point was 11 October 2021. Studies were included if they were observational in design (excluding case reports and case series), and involved at least one patient who experienced myocarditis, pericarditis, or myopericarditis following any mRNA COVID-19 vaccine (any case definition was accepted). Pre-print manuscripts were included if no peer-reviewed version was available. Studies of other designs and studies investigating other vaccines were excluded. Studies investigating cardiac effects of SARS-CoV-2 infection were excluded. No restrictions on language or date were applied.

The search terms used were:

(myocarditis OR pericarditis OR myopericarditis) AND (covid-19) AND (vaccine)

Data were extracted for study design, study period, vaccine of interest, population, number of cases of myocarditis or pericarditis, and where specified the percentage of cases who were male, age, and the vaccine dose after which the event occurred. One reviewer extracted data. These data were tabulated.

Study quality was assessed by one reviewer, using the relevant Critical Appraisal Skills Programme (CASP) tool (criteria not presented) (33). Each checklist covers a different study design and contains a series of questions to critically appraise the research.

2.2 Updating the Review

This is intended to be a “living” systematic review. We will provide an update when new information or publications are released which significantly impacts our conclusions. At this time, systematic literature searches using the above search terms and criteria will be run and spontaneously reported data will be updated.

Results and conclusions will be updated if new pharmacoepidemiological evidence has been released. Due to the nature of spontaneous reporting (i.e. events counts change daily), this data will be updated at the same time as the systematic literature review. Updates to the results and conclusions will be submitted as letter to the editor communications, to be used as an addendum to the original manuscript. Each update will cite the original manuscript and previously published updates.

2.3 Patient and Public Involvement

Patients and the public were not consulted during this study.

3.0 Results

Overall, across the three spontaneous reporting databases examined, there were a total of 5295 events of myocarditis and 3453 reports of pericarditis submitted to the regulators up to 21 October 2021. Of the reported events of myocarditis, 3883 (73.3%) concerned Comirnaty, whereas 75.9% of all pericarditis reports (n=2620 of 3453 reports) followed the Comirnaty vaccine.

Sex and age data were only available for the VAERS and EudraVigilance populations (Figure 1). Age was skewed towards younger vaccinees for both myocarditis and pericarditis following Comirnaty and Spikevax for the VAERS and EudraVigilance populations (Figure 1). In these populations, males represented 74.9% (n=3641 of 4860) of all myocarditis reports and 56.9% (n=1778 of 3126) of all pericarditis reports.

3.1 United Kingdom

Data reported to MHRA's Yellow Card scheme was available from the data of each vaccine's authorisation to 20 October 2021 (3). Overall, 435 reports of myocarditis and 327 reports of pericarditis had been submitted to the Yellow Card scheme from the date of vaccine launch to 20 October 2021. Of these, there were 350 reported myocarditis events and 274 pericarditis events reported to Yellow Card scheme up to and including 20 October 2021 following Comirnaty (Table 1). Two of these events were reported to have a fatal outcome (n=1 each for myocarditis and pericarditis). For Spikevax, 85 reports of myocarditis and 53 reports of pericarditis had been submitted to the Yellow Card scheme up to 20 October 2021; none of these events had a fatal outcome (Table 1). No data was available on the age or sex of those reporting events, or on which dose of the vaccine each event occurred.

As of 20 October 2021, it was estimated that 23.2 million first doses and 20.1 million second doses of Comirnaty had been administered in the UK (3). Therefore, there were approximately 15.09 cases of myocarditis and 11.81 cases of pericarditis per million vaccinees who had received at least one dose of Comirnaty. To the same date, approximately 1.5 million first doses and 1.3 million second doses of Spikevax had also been administered (3). Therefore, of those who had received at least one dose of Spikevax in the UK, 56.67 cases of myocarditis and 40.77 cases of pericarditis had been reported per million vaccinated.

3.2 United States

To 21 October 2021, there had been 1314 events of myocarditis reported following the Comirnaty overall (Table 2). Of these, 1001 (76.18%) had occurred in males (Table 2). There was evidence of a higher frequency of reports for younger age groups amongst both males and females, with a decreasing number of reports with increasing age (Table 2). While pericarditis was again more frequently reported in males (n=539; 65.97% of 817 reported events) following Comirnaty, for vaccinees over 40 years of age the pattern was less pronounced (Table 2). For Spikevax, similar trends were observed. Of the 622 events of myocarditis reported to VAERS following Spikevax, 73.47% (n=457) occurred in males, with more frequent reports in younger age groups (Table 2). Similarly, 58.81% of the total 454

reported pericarditis events occurred in males, however for pericarditis the trend in age was less distinct (Table 2).

The majority of both myocarditis and pericarditis reported events occurred after the second dose of Comirnaty (Table 3a) and Spikevax (Table 3b). For Comirnaty, of the total 1314 reported events of myocarditis, 771 (58.68%) were reported following the second dose while 280 (21.31%) were reported after a single dose of the vaccine (Table 3a). Similarly, 53.00% of events of pericarditis were reported following two doses of Comirnaty (n=433 of 817 reported events; Table 3a). For Spikevax, 291 of 622 (46.78%) reported events of myocarditis and 229 of the 454 (50.44%) reported events of pericarditis occurred following two doses of the vaccine (Table 3b). A small number of reports of myocarditis and pericarditis had been reported following a third dose for both vaccines (Tables 3a and 3b).

In the US, there had been 104.98 million vaccinees who had received the full two-dose regimen of Comirnaty (27); therefore, there were 12.52 cases of myocarditis reported per million and 7.78 cases of pericarditis per million fully vaccinated individuals. There had been 69.70 million people fully vaccinated with Spikevax (27); therefore, there were 8.92 cases of myocarditis reported per million fully vaccinated Spikevax recipients and 6.51 cases of pericarditis per million fully vaccinated Spikevax vaccinees.

3.3 European Economic Area

To 21 October 2021, there had been a total of 2219 reports of myocarditis and 1529 reports of pericarditis to EurdraVigilance from the EEA, following Comirnaty. Following Spikevax, there were 705 reports of myocarditis and 326 reports of pericarditis submitted to EudraVigilance up to 21 October 2021 (Table 4). For both mRNA vaccines, 76.03% of the reported myocarditis events from the EEA were reported in males. Meanwhile, 52.40% of pericarditis events reported to EudraVigilance following mRNA vaccines were reported in males.

There were 15 reports of myocarditis and five reports of pericarditis which had a fatal outcome following Comirnaty, and four fatal reports of myocarditis and one of pericarditis following Spikevax. Most of these fatal events were in males (16 of 25 reports with fatal outcomes overall; 64.00%).

To the week ending 17 October 2021, approximately 267.48 million first doses of Comirnaty had been administered throughout the EU and EEA (28). Therefore, there were approximately 8.30 cases of myocarditis and 5.72 cases of pericarditis reported per million vaccinees who had received at least one dose of Comirnaty. Spikevax had been administered to considerably fewer vaccinees up to the same date, with a total 40.02 million first doses given in the European Union and EEA (28). There were 17.62 cases of myocarditis and 8.15 cases of pericarditis per million vaccinees who had received at least one dose of Spikevax.

3.4 Systematic literature review

There were 253 studies identified by the search within PubMed/Medline and Embase databases. Following de-duplication of manuscripts there were 175 papers which underwent screening. After applying exclusion criteria, seven published epidemiological studies were included in the systematic literature review portion of this study (29-35). Table 5 outlines the study design, study period, vaccines under observation, study population, and the frequency and demographics of myocarditis or pericarditis cases within each study. All observational designs in all populations were considered, therefore meta-analyses or pooling of results were not appropriate.

Studies were assessed for quality using the most appropriate CASP checklist (36). One reviewer assessed quality, using questions within the checklist. All studies were considered of sufficient quality to be included (data not shown).

Results of all studies were consistent. Where reported, males represented 80-100% of the study populations (Table 5). The age ranges of myocarditis cases varied, however in three of the four studies where ages were reported, cases appeared to occur most frequently in younger patients (under the age of 40 years) (32, 34, 35). In the fourth study, post-mortem examination revealed myocarditis as the cause of death in one 65-year-old male (33). This patient had pre-existing cardiac disease, therefore it was not conclusively determined whether exposure to the vaccine resulted in this patient's death (33).

4.0 Discussion

There have been a small number of reports of myocarditis and pericarditis following exposure to mRNA COVID-19 vaccines in each database examined, considering the number of people who have received a COVID-19 vaccine in each region. In all spontaneous reporting systems and for both mRNA vaccines, the reporting rate of myocarditis was higher than that of pericarditis. This may be true, or it may also reflect that the diagnosis of myocarditis is relatively more straightforward. In the UK and EU/EEA, reporting rates of myocarditis and pericarditis were higher following Spikevax compared with those for Comirnaty. However, the opposite was observed for the US. A full dose of Spikevax used for first and second doses contains 100 micrograms of mRNA nucleotides, whereas a full dose of Comirnaty contains 30 micrograms of the mRNA material (10, 11). This is one possible reason for the higher reporting rate of myocarditis and pericarditis observed for Spikevax in the UK population. A half dose of Spikevax is used for third vaccination doses; this still contains more genetic material than Comirnaty (10). Therefore, it will become increasingly important as more people receive third booster doses of mRNA COVID-19 vaccines to monitor the frequency and severity of myocarditis and pericarditis following exposure to these vaccines.

The UK had the highest reporting rate for both myocarditis and pericarditis following mRNA vaccines, particularly for events following Spikevax. Reporting rates for the US and EU/EEA regions were similar for each event following each vaccine. It is possible that the UK and EU/EEA have stronger spontaneous reporting systems compared with the US, which may explain the higher reporting rates observed for this population. The frequency of events noted by regulators, the World Health Organisation, and in the vaccines' summaries of product characteristics (SmPC) suggest that myocarditis and pericarditis are very rare, occurring in less than one in 10,000 vaccine doses administered (2, 3, 7, 12, 13).

Our calculated reporting rates for myocarditis and pericarditis following mRNA vaccines in each of the UK, US, and EU/EEA were consistent with this. However, underreporting of the events to regulators is possible, therefore it may be that the events of myocarditis and pericarditis are 'rare' events (more frequent than 1/10,000) rather than 'very rare' (less frequent than 1/10,000) events as suggested. In October 2021, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency announced a plan to review the risk of myocarditis and pericarditis following mRNA vaccines (37). It is therefore possible that updates to the vaccines' SmPC will be required once this review is complete.

When examining the demographics of vaccinees who had reported myocarditis or pericarditis following mRNA vaccines, both events appear to more commonly affect males compared with females, particularly amongst vaccinees of younger age categories (Tables 2-4). This is consistent with early reports surrounding these events, where it was suggested that younger males appear at higher risk of myocarditis and pericarditis following mRNA vaccines (4). Demographic data was available for VAERS and EudraVigilance populations; in these databases results were similar with more than 70% of myocarditis and more than 50% of pericarditis events reported in males (Tables 2 and 4). These results are consistent with results of pharmacoepidemiological studies in the published literature; in the studies where sex was reported, more than 80% of patients were male and most patients were under the age of 40 years (Table 5) (30-35). This is an interesting finding, as it has been previously suggested that over 70% of reports to VAERS involve females (31). It is possible that the event was missed or misclassification occurred in older adults, particularly in older individuals in the three populations of interest who were vaccinated prior to the signal emerging. It is also possible that some of the symptoms of myocarditis and pericarditis, for example chest pain and breathlessness, were attributed to other cardio-respiratory conditions in older people. Nonetheless, it is known that most cases of myocarditis (any cause) occur in young adults, with males more commonly affected than females; this supports the results observed in this study (38, 39). Alternatively, vaccine roll-out in each of the regions may have affected the results observed in some of the countries; in the UK, mRNA vaccines were more frequently used in younger age groups, while older vaccinees may have been more likely to receive an adenovirus vector vaccine.

Data on vaccine dose were only available from the VAERS database. Most cases reported to VAERS to be reported following a second dose of vaccine (Tables 3a and 3b). This is consistent with the early signal which emerged in Israel, where 121 of the 148 reported cases of myocarditis occurred around the time of the second dose of COVID-19 vaccine (4). Furthermore, similar results were observed by Hajjo et al., who found only a very small number of events occurring after a third dose in their analysis of VAERS data (40).

Pharmacoepidemiological studies identified by systematic review (Table 5) were consistent with results found in spontaneously data from VAERS and EudraVigilance (Tables 2-5). Young males more frequently reported myocarditis in each of these studies and found in our analysis of spontaneous reporting data. Furthermore, reports were more frequent following a second dose of mRNA vaccine.

Myocarditis has been observed historically following vaccination, including after smallpox, influenza, and hepatitis B vaccines; prior to COVID-19, 0.1% of reports to VAERS between 1990 and 2018 had been in relation to myopericarditis (5). Furthermore, myocarditis is known to occur after a range of viral infections, including coronaviruses which cause Middle East Respiratory Syndrome (MERS) and COVID-19, with viral infection the most

common cause of myocarditis (41-43). This study provides evidence that younger vaccinees more frequently report myocarditis and pericarditis following mRNA COVID-19 vaccines compared with older vaccinees, and reports are more frequent following the second dose. Results were consistent between each of the three data sources used. This is an important finding, because as vaccination programmes around the world progress, rates of myocarditis and pericarditis are likely to increase. The effect of booster vaccinations with mRNA COVID-19 vaccines on the development of myocarditis and pericarditis is largely unknown. Furthermore, mRNA COVID-19 vaccines (particularly Spikevax) will be supplied to the COVAX initiative for distribution throughout low- and middle-income countries, where diagnostic imaging and access to healthcare is more difficult (44, 45). Regulatory authorities should continue to monitor the effect of mRNA vaccination might have on the heart in the populations for which they are responsible. The proportions of young people are higher in low- and middle-income countries' populations compared to high income countries. Issuing diagnostic criteria and treatment protocols for myocarditis and pericarditis with mRNA COVID-19 vaccines that take into consideration the capabilities of the local healthcare system.

4.1 Limitations

Vaccination policies in the three regions may have biased the results towards a higher number of adverse events reports myocarditis and pericarditis from younger vaccinees compared with older vaccinees. In each of these regions, younger people were more likely to have received mRNA vaccines, which may have contributed to higher reporting rates of myocarditis and pericarditis in younger vaccinees. The frequency of reported events per age group was presented as a crude number, and reporting rates could only be calculated as an overall estimate rather than stratified by age; based on the data available for vaccinations administered, it was not possible to determine the proportion of all vaccinees per age group who reported an event of myocarditis or pericarditis. This is very important, because it is likely that the reporting rate of myocarditis and pericarditis with mRNA COVID-19 vaccines will be higher in young people and even higher in young men if the reporting rates are stratified by age and sex. The regulatory authorities and Marketing Authorisations Holders (MAHs) need to follow up reports of these conditions with reporters to obtain as much information and make this information available publicly. Myocarditis and pericarditis following mRNA COVID-19 vaccines is an area which requires further research.

The data sources for this study were spontaneous reporting systems of the UK, US, and EEA. All spontaneous reporting systems have well-known limitations including missing information, and reporting bias caused by publicity surrounding a particular adverse event. (46). Misclassification of myocarditis and pericarditis is also possible particularly before these events attracted publicity or among older age groups. Under-reporting is a major limitation of spontaneous reporting; even with the intense publicity and global attention on COVID-19 vaccine safety, it is possible that not all cases are reported to regulatory authorities (47, 48). Furthermore, a report to spontaneous reporting systems indicates suspicion that the event was associated with the vaccine, it does not confirm that the vaccine caused the event (3, 46). Further assessment is required to determine causality for each report. Finally, it is not possible to estimate incidence rates using spontaneous reports, and there is no unvaccinated comparison group (46).

Using publicly available data introduced some challenges, as the level of detail available was limited and varied between data sources. The MHRA does not publish detail on each of the reported events, including demographics of the vaccinees in which reported events occur. Furthermore, data on the vaccine dose on which the reported events of myocarditis and pericarditis occurred were only available for the US VAERS population. Information contained within individual reports is not routinely made available, however these comprise important clinical information that would allow better understanding of each case. Such details should be made publicly available. Better transparency is needed to allow more robust research using spontaneous reporting to be undertaken.

Due to the limited published research into myocarditis and pericarditis following mRNA COVID-19 vaccines, we included all pharmacoepidemiological study designs (except case reports and case series) and considered all study populations and all study periods for inclusion. The purpose of systematically reviewing the literature was to determine whether results from our analyses of spontaneous reports were consistent with other evidence currently available. Due to the heterogenous nature of the included studies, no pooling of data, syntheses, or meta-analyses could be completed. It should be noted that there were no formal assessments of publication bias during the systematic literature review. However, a CASP checklist was completed for each included study, which deemed the research to be of sufficient quality for inclusion. Nonetheless, each study had limitations which should be considered when interpreting their results. The possibility of publication bias was not formally analysed.

Further pharmacoepidemiological studies are urgently needed to address many of the limitations of spontaneous reporting in understanding myocarditis and pericarditis following mRNA COVID-19 vaccines including more accurate estimates of the frequency, better understanding of the clinical course and the effects of these on quality of life. It is also important to compare the incidence and characteristics of these events with recipients of other non-mRNA COVID-19 vaccines and unvaccinated people. However, these studies will take time to be conducted.

5.0 Conclusions

This study adds to existing evidence that younger vaccinees more frequently report myocarditis and pericarditis following mRNA COVID-19 vaccines compared with older vaccinees, and reports are more frequent following the second dose. These events are very rare or possibly rare according to the estimated reporting rates from spontaneous adverse reactions. The events were more frequently reported amongst males, and most reports came from vaccinees aged under 30 years. The clinical course of these events is typically mild, with full recovery in most cases.

The study brings together spontaneously reported adverse event data from three regions. Consistencies in the reporting rates and trends of myocarditis and pericarditis within the three data sources utilised suggest that results may be generalisable to other populations in which mRNA vaccines are used. However, limitations of the data sources used and biases which may have affected results should be considered. It is important that regulatory authorities continue to monitor the effects of mRNA vaccines on the heart, particularly as vaccine programmes progress to include younger vaccinees in many parts of the world. Myocarditis and pericarditis following mRNA COVID-19 vaccines is an area which requires further research, especially in children and adolescents and following a third (booster)

dose. Pharmacoepidemiological studies are urgently needed to address many of the limitations of spontaneous reporting in understanding myocarditis and pericarditis following mRNA Covid-19 vaccines including more accurate estimates of frequency, a better understanding of the clinical course, and the effects on quality of life. However, they will take time to be conducted.

Declarations

Transparency statement

The manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, and that no important aspects of the study have been omitted.

Ethics approval

Ethics approval was not required.

Funding

No external funding was received for the preparation of this manuscript.

Conflicts of interest

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: The Drug Safety Research Unit (DSRU) is a registered independent charity (No. 327206) associated with the University of Portsmouth. The DSRU receives donations and grants from pharmaceutical companies; however, the companies have no control over the conduct or publication of its studies. The DSRU has received grants to conduct unconditional studies on the Oxford/AstraZeneca COVID-19 vaccine and is in negotiations to receiving grants for conducting CPRD studies for Pfizer, Moderna, and Janssen COVID-19 vaccines. The DSRU has conducted benefit-risk studies on products for COVID-19, including remdesivir, lopinavir/ritonavir, chloroquine and hydroxychloroquine, and convalescent plasma. Professor Shakir is the principal investigator for an active surveillance study for the Oxford/AstraZeneca vaccine, but this assessment is unrelated to this study. Professor Shakir has been a member of Data Safety Monitoring Boards for Ipsen, Biogen, and Diurnal. None of these companies have any involvement with COVID-19 vaccines. Professor Shakir was invited by AstraZeneca to advise on the events of thrombosis with thrombocytopenia with the COVID-19 vaccine and to be a member of an advisory committee on a safety study of the Oxford/AstraZeneca vaccine in Europe. Samantha Lane and Alison Yeomans have no conflicts of interest with regard to this study.

Authors' contributions

SL was responsible for data acquisition, analyses, and interpretation. SL, AY, and SS were responsible for study conception, drafting and reviewing the manuscript, and approval of the final version for publication.

Data sharing

CASP checklists for assessing quality of each study included in systematic review are available on request.

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Table 1: Myocarditis and Pericarditis events reported Yellow Card. Datalock point 20 October 2021.

Vaccine	Myocarditis reported events	Myocarditis reports with fatal outcome	Pericarditis reported events	Pericarditis reports with fatal outcome	Total reported events	Total reports with fatal outcome
	n	n	n	n	N	N
Comirnaty (Pfizer/BioNTech)	350	1	274	1	624	2
Spikevax (Moderna)	85	0	53	0	138	0
Overall	423	1	317	1	740	2

Table 2: Myocarditis and pericarditis events reported to VAERS overall. Datalock point 21 October 2021. Percentages per age group are presented.

Age Group	Myocarditis								Pericarditis							
	Male		Female		Sex Not Specified		Total		Male		Female		Sex Not Specified		Total	
	n	%	n	%	n	%	N	%	n	%	n	%	n	%	N	%
Comirnaty																
6-17 Years	420	88.42	53	11.16	2	0.42	475	100.00	117	86.67	17	12.59	1	0.74	135	100.00
18-29 Years	320	82.90	65	16.84	1	0.26	386	100.00	168	86.15	27	13.85	0	0.00	195	100.00
30-39 Years	96	68.57	44	31.43	0	0.00	140	100.00	86	68.25	40	31.75	0	0.00	126	100.00
40-49 Years	52	57.78	38	42.22	0	0.00	90	100.00	36	43.37	47	56.63	0	0.00	83	100.00
50-59 Years	26	40.63	38	59.38	0	0.00	64	100.00	49	46.67	56	53.33	0	0.00	105	100.00
60-64 Years	8	32.00	15	60.00	2	8.00	25	100.00	16	33.33	32	66.67	0	0.00	48	100.00
65-79 Years	28	56.00	22	44.00	0	0.00	50	100.00	51	57.95	36	40.91	1	1.14	88	100.00
80+ Years	1	33.33	2	66.67	0	0.00	3	100.00	5	50.00	5	50.00	0	0.00	10	100.00
Not Specified	50	61.73	17	20.99	14	17.28	81	100.00	11	40.74	14	51.85	2	7.41	27	100.00
Total	1001	76.18	294	22.37	19	1.45	1314	100.00	539	65.97	274	33.54	4	0.49	817	100.00
Spikevax																
6-17 Years	4	80.00	1	20.00	0	0.00	5	100.00	1	100.00	0	0.00	0	0.00	1	100.00
18-29 Years	245	85.96	40	14.04	0	0.00	285	100.00	94	76.42	29	23.58	0	0.00	123	100.00
30-39 Years	91	75.21	30	24.79	0	0.00	121	100.00	45	65.22	24	34.78	0	0.00	69	100.00
40-49 Years	45	64.29	25	35.71	0	0.00	70	100.00	36	51.43	34	48.57	0	0.00	70	100.00
50-59 Years	23	53.49	19	44.19	1	2.33	43	100.00	34	53.13	30	46.88	0	0.00	64	100.00
60-64 Years	8	36.36	14	63.64	0	0.00	22	100.00	16	47.06	18	52.94	0	0.00	34	100.00
65-79 Years	19	54.29	16	45.71	0	0.00	35	100.00	30	48.39	31	50.00	1	1.61	62	100.00

80+ Years	4	57.14	3	42.86	0	0.00	7	100.00	5	38.46	8	61.54	0	0.00	13	100.00
Not Specified	18	52.94	2	5.88	14	41.18	34	100.00	6	33.33	4	22.22	8	44.44	18	100.00
Total	457	73.47	150	24.12	15	2.41	622	100.00	267	58.81	178	39.21	9	1.98	454	100.00
Overall (both mRNA vaccines)																
6-17 Years	424	88.33	54	11.25	2	0.42	480	100.00	118	86.76	17	12.50	1	0.74	136	100.00
18-29 Years	565	84.20	105	15.65	1	0.15	671	100.00	262	82.39	56	17.61	0	0.00	318	100.00
30-39 Years	187	71.65	74	28.35	0	0.00	261	100.00	131	67.18	64	32.82	0	0.00	195	100.00
40-49 Years	97	60.63	63	39.38	0	0.00	160	100.00	72	47.06	81	52.94	0	0.00	153	100.00
50-59 Years	49	45.79	57	53.27	1	0.93	107	100.00	83	49.11	86	50.89	0	0.00	169	100.00
60-64 Years	16	34.04	29	61.70	2	4.26	47	100.00	32	39.02	50	60.98	0	0.00	82	100.00
65-79 Years	47	55.29	38	44.71	0	0.00	85	100.00	81	54.00	67	44.67	2	1.33	150	100.00
80+ Years	5	50.00	5	50.00	0	0.00	10	100.00	10	43.48	13	56.52	0	0.00	23	100.00
Not Specified	68	59.13	19	16.52	28	24.35	115	100.00	17	37.78	18	40.00	10	22.22	45	100.00
Total	1458	75.31	444	22.93	34	1.76	1936	100.00	806	63.41	452	35.56	13	1.02	1271	100.00

Table 3a: Myocarditis and pericarditis events reported to VAERS following Pfizer/BioNTech COVID-19 vaccine (Comirnaty), by dose. Datalock point 21 October 2021. Percentages per age group are presented.

Age Group	Myocarditis								Pericarditis							
	Male		Female		Sex Not Specified		Total		Male		Female		Sex Not Specified		Total	
	n	%	n	%	n	%	N	%	n	%	n	%	n	%	N	%
Dose 1																
6-17 Years	78	89.66	9	10.34	0	0.00	87	100.00	21	75.00	7	25.00	0	0.00	28	100.00
18-29 Years	55	78.57	15	21.43	0	0.00	70	100.00	41	73.21	15	26.79	0	0.00	56	100.00
30-39 years	22	52.38	20	47.62	0	0.00	42	100.00	30	62.50	18	37.50	0	0.00	48	100.00
40-49 years	8	42.11	11	57.89	0	0.00	19	100.00	9	37.50	15	62.50	0	0.00	24	100.00
50-59 years	6	31.58	13	68.42	0	0.00	19	100.00	17	44.74	21	55.26	0	0.00	38	100.00
60-64 years	2	28.57	5	71.43	0	0.00	7	100.00	4	23.53	13	76.47	0	0.00	17	100.00
65-79 Years	10	52.63	9	47.37	0	0.00	19	100.00	20	64.52	11	35.48	0	0.00	31	100.00
80+ Years	0	0.00	2	100.00	0	0.00	2	100.00	2	66.67	1	33.33	0	0.00	3	100.00
Not Specified	8	53.33	6	40.00	1	6.67	15	100.00	2	50.00	2	50.00	0	0.00	4	100.00
Total	189	67.50	90	32.14	1	0.36	280	100.00	146	58.63	103	41.37	0	0.00	249	100.00
Dose 2																
6-17 Years	264	88.29	34	11.37	1	0.33	299	100.00	79	89.77	9	10.23	0	0.00	88	100.00
18-29 Years	185	83.33	36	16.22	1	0.45	222	100.00	89	91.75	8	8.25	0	0.00	97	100.00
30-39 years	56	72.73	21	27.27	0	0.00	77	0.00	47	71.21	19	28.79	0	0.00	66	100.00
40-49 years	34	59.65	23	40.35	0	0.00	57	0.00	20	43.48	26	56.52	0	0.00	46	100.00
50-59 years	15	41.67	21	58.33	0	0.00	36	0.00	25	47.17	28	52.83	0	0.00	53	100.00
60-64 years	4	44.44	5	55.56	0	0.00	9	0.00	7	33.33	14	66.67	0	0.00	21	100.00

65-79 Years	13	56.52	10	43.48	0	0.00	23	0.00	24	58.54	16	39.02	1	2.44	41	100.00
80+ Years	1	100.00	0	0.00	0	0.00	1	0.00	3	50.00	3	50.00	0	0.00	6	100.00
Not Specified	38	80.85	6	12.77	3	6.38	47	100.00	5	33.33	8	53.33	2	13.33	15	100.00
Total	610	79.12	156	20.23	5	0.65	771	100.00	299	69.05	131	30.25	3	0.69	433	100.00
Dose 3																
6-17 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
18-29 Years	0	0.00	0	0.00	0	0.00	0	0.00	1	100.00	0	0.00	0	0.00	1	100.00
30-39 years	2	100.00	0	0.00	0	0.00	2	100.00	0	0.00	0	0.00	0	0.00	0	0.00
40-49 years	0	0.00	1	100.00	0	0.00	1	100.00	0	0.00	0	0.00	0	0.00	0	0.00
50-59 years	0	0.00	0	0.00	0	0.00	0	0.00	1	50.00	1	50.00	0	0.00	2	100.00
60-64 years	1	50.00	1	0.00	0	0.00	2	100.00	0	0.00	1	100.00	0	0.00	1	100.00
65-79 Years	4	100.00	0	0.00	0	0.00	4	100.00	3	100.00	0	0.00	0	0.00	3	100.00
80+ Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Not Specified	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total	7	77.78	2	22.22	0	0.00	9	100.00	5	71.43	2	28.57	0	0.00	7	100.00
Unknown dose																
6-17 Years	78	87.64	10	11.24	1	1.12	89	100.00	17	89.47	1	5.26	1	5.26	19	100.00
18-29 Years	80	85.11	14	14.89	0	0.00	94	100.00	37	90.24	4	9.76	0	0.00	41	100.00
30-39 years	16	84.21	3	15.79	0	0.00	19	100.00	9	75.00	3	25.00	0	0.00	12	100.00
40-49 years	10	76.92	3	23.08	0	0.00	13	100.00	7	53.85	6	46.15	0	0.00	13	100.00
50-59 years	5	55.56	4	44.44	0	0.00	9	100.00	6	50.00	6	50.00	0	0.00	12	100.00
60-64 years	1	14.29	4	57.14	2	28.57	7	100.00	5	55.56	4*	44.44	0	0.00	9	100.00
65-79 Years	1	25.00	3	75.00	0	0.00	4	100.00	4	30.77	9	69.23	0	0.00	13	100.00
80+ Years	0	0.00	0	0.00	0	0.00	0	100.00	0	0.00	1	100.00	0	0.00	1	100.00
Not Specified	0	0.00	0	0.00	0	0.00	0	100.00	4	50.00	4	50.00	0	0.00	8	100.00

Total	191	81.28	41	17.45	3	1.28	235	100.00	89	69.53	38	29.69	1	0.78	128	100
*Includes 2 reported events occurring after reported 5 doses																

Table 3b: Myocarditis and pericarditis events reported to VAERS following Moderna COVID-19 vaccine (Spikevax), by dose. Datalock point 21 October 2021. Percentages per age group are presented.

Age Group	Myocarditis								Pericarditis							
	Male		Female		Sex Not Specified		Total		Male		Female		Sex Not Specified		Total	
	n	%	n	%	n	%	N	%	n	%	n	%	n	%	N	%
Dose 1																
6-17 Years	1	100.00	0	0.00	0	0.00	1	0.00	0	0.00	0	0.00	0	0.00	0	0.00
18-29 Years	61	83.56	12	16.44	0	0.00	73	100.00	25	67.57	12	32.43	0	0.00	37	100.00
30-39 years	34	69.39	15	30.61	0	0.00	49	100.00	13	52.00	12	48.00	0	0.00	25	100.00
40-49 years	11	55.00	9	45.00	0	0.00	20	100.00	16	53.33	14	46.67	0	0.00	30	100.00
50-59 years	12	57.14	8	38.10	1	4.76	21	100.00	10	47.62	11	52.38	0	0.00	21	100.00
60-64 years	4	30.77	9	69.23	0	0.00	13	100.00	4	40.00	6	60.00	0	0.00	10	100.00
65-79 Years	8	50.00	8	50.00	0	0.00	16	100.00	7	38.89	10	55.56	1	5.56	18	100.00
80+ Years	2	66.67	1	33.33	0	0.00	3	100.00	0	0.00	4	100.00	0	0.00	4	100.00
Not Specified	14	70.00	0	0.00	6	30.00	20	100.00	3	37.50	3	37.50	2	25.00	8	100.00
Total	147	68.06	62	28.70	7	3.24	216	100.00	78	50.98	72	47.06	3	1.96	153	100.00
Dose 2																
6-17 Years	2	100.00	0	0.00	0	0.00	2	100.00	1	100.00	0	0.00	0	0.00	1	100.00
18-29 Years	131	85.06	23	14.94	0	0.00	154	100.00	54	83.08	11	16.92	0	0.00	65	100.00
30-39 years	40	81.63	9	18.37	0	0.00	49	100.00	25	71.43	10	28.57	0	0.00	35	100.00
40-49 years	23	60.53	15	39.47	0	0.00	38	100.00	15	48.39	16	51.61	0	0.00	31	100.00
50-59 years	9	56.25	7	43.75	0	0.00	16	100.00	18	52.94	16	47.06	0	0.00	34	100.00
60-64 years	3	50.00	3	50.00	0	0.00	6	100.00	7	43.75	9	56.25	0	0.00	16	100.00

65-79 Years	11	64.71	6	35.29	0	0.00	17	100.00	18	51.43	17	48.57	0	0.00	35	100.00
80+ Years	1	50.00	1	50.00	0	0.00	2	100.00	4	50.00	4	50.00	0	0.00	8	100.00
Not Specified	2	28.57	1	14.29	4	57.14	7	100.00	2	50.00	1	25.00	1	25.00	4	100.00
Total	222	76.29	65	22.34	4	1.37	291	100.00	144	62.88	84	36.68	1	0.44	229	100.00
Dose 3																
6-17 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
18-29 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
30-39 years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	100.00	0	0.00	1	100.00
40-49 years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
50-59 years	0	0.00	3	100.00	0	0.00	3	100.00	0	0.00	0	0.00	0	0.00	0	0.00
60-64 years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
65-79 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
80+ Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Not Specified	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total	0	0.00	3	100.00	0	0.00	3	100.00	0	0.00	1	100.00	0	0.00	1	100.00
Unknown dose																
6-17 Years	1	50.00	1	50.00	0	0.00	2	100.00	0	0.00	0	0.00	0	0.00	0	0.00
18-29 Years	53	91.38	5	8.62	0	0.00	58	100.00	15	71.43	6	28.57	0	0.00	21	100.00
30-39 years	17	73.91	6	26.09	0	0.00	23	100.00	7	87.50	1	12.50	0	0.00	8	100.00
40-49 years	11	91.67	1	8.33	0	0.00	12	100.00	5	55.56	4	44.44	0	0.00	9	100.00
50-59 years	2	40.00	3	60.00	0	0.00	5	100.00	6	66.67	3	33.33	0	0.00	9	100.00
60-64 years	1	33.33	2	66.67	0	0.00	3	100.00	5	62.50	3	37.50	0	0.00	8	100.00
65-79 Years	0	0.00	2	100.00	0	0.00	2	100.00	5	55.56	4	44.44	0	0.00	9	100.00
80+ Years	1	50.00	1	50.00	0	0.00	2	100.00	1	100.00	0	0.00	0	0.00	1	100.00
Not Specified	2	28.57	1	14.29	4	57.14	7	100.00	1	20.00	0	0.00	4	80.00	5	100.00

Total	88	77.19	22	19.30	4	3.51	114	100.00	45	64.29	21	30.00	4	5.71	70	100.00

Table 4: Myocarditis and pericarditis events reported to EudraVigilance for the European Economic Area. Datalock point 21 October 2021. Percentages per age group are presented.

Age Group	Myocarditis								Pericarditis							
	Male		Female		Sex Not Specified		Total		Male		Female		Sex Not Specified		Total	
	n	%	n	%	n	%	N	%	n	%	n	%	n	%	N	%
Comirnaty																
12-17 Years	256	85.91	37	12.42	5	1.68	298	100.00	44	61.11	28	38.89	0	0.00	72	100.00
18-64 Years	1251	73.89	431	25.46	11	0.65	1693	100.00	606	49.67	610	50.00	4	0.33	1220	100.00
65-85 Years	69	51.49	65	48.51	0	0.00	134	100.00	109	57.37	81	42.63	0	0.00	190	100.00
Over 85 Years	6	50.00	6	50.00	0	0.00	12	100.00	14	63.64	8	36.36	0	0.00	22	100.00
Not Specified	57	69.51	21	25.61	4	4.88	82	100.00	13	52.00	12	48.00	0	0.00	25	100.00
Total	1639	73.86	560	25.24	20	0.90	2219	100.00	786	51.41	739	48.33	4	0.26	1529	100.00
Spikevax																
12-17 Years	29	100.00	0	0.00	0	0.00	29	100.00	4	100.00	0	0.00	0	0.00	4	100.00
18-64 Years	540	83.20	106	16.33	3	0.46	649	100.00	163	58.63	112	40.29	3	1.08	278	100.00
65-85 Years	10	50.00	10	50.00	0	0.00	20	100.00	16	43.24	21	56.76	0	0.00	37	100.00
Over 85 Years	0	0.00	1	100.00	0	0.00	1	100.00	0	0.00	2	100.00	0	0.00	2	100.00
Not Specified	5	83.33	1	16.67	0	0.00	6	100.00	3	60.00	2	40.00	0	0.00	5	100.00
Total	584	82.84	118	16.74	3	0.43	705	100.00	186	57.06	137	42.02	3	0.92	326	100.00
Overall (both mRNA vaccines)																
12-17 Years	285	87.16	37	11.31	5	1.53	327	100.00	48	63.16	28	36.84	0	0.00	76	100.00
18-64 Years	1791	76.47	537	22.93	14	0.60	2342	100.00	769	51.34	722	48.20	7	0.47	1498	100.00
65-85 Years	79	51.30	75	48.70	0	0.00	154	100.00	125	55.07	102	44.93	0	0.00	227	100.00

Over 85 Years	6	46.15	7	53.85	0	0.00	13	100.00	14	58.33	10	41.67	0	0.00	24	100.00
Not Specified	62	70.45	22	25.00	4	4.55	88	100.00	16	53.33	14	46.67	0	0.00	30	100.00
Total	2223	76.06	678	23.19	23	0.79	2924	100.00	972	52.40	876	47.22	7	0.38	1855	100.00

Table 5: Details of each study identified by systematic review which met the inclusion criteria.

Author/Citation	Study period	Study design	Vaccine	Population	Condition	Cases	Age	Sex (% who are male)	Dose
Furer et al. **(29)**	12/2020 – 03/2021	Multicentre cohort study	Comirnaty (2 doses)	Adults with autoimmune inflammatory rheumatic diseases (n=670) and healthy controls (n=121) at the Rheumatology Departments of Tel Aviv Sourasky, Carmel, and Hadassah Medical Center, Israel	Pericarditis	1 case of pericarditis in autoimmune diseases group	NR	NR	2
Mevorach et al. **(30)**	20/12/2020 – 31/5/2021	Retrospective review of medical records	Comirnaty	Israeli residents included in wider vaccine safety surveillance	Myocarditis	19 117	NR	89.5% 86.3%	1 2
Rose et al. **(31)**	Up to 9/7/2021	Analysis of VAERS data	Comirnaty, Spikevax, Johnson & Johnson	Adolescents (aged 12-15 years) and adults reporting to VAERS	Myocarditis	559	NR	80%	NR*

Schauer et al. **(32)**	1/4/2021 – 21/6/2021	Retrospective review of medical records	Comirnaty (2 doses)	Adolescents aged 12-17 years, admitted to Seattle Children's Hospital, Washington State, US	Myopericarditis	13	Median 15 years	92.3%	2
Schneider et al. **(33)**	11/3/2021 – 9/6/2021	Postmortem investigation	Any COVID-19 vaccine	Catchment of Bielefeld, Detmold & Münster Public Prosecutor's Offices, Germany	Myocarditis	1	65 years old	100%	1 dose of Pfizer
Simone et al. **(34)**	14/12/2020 – 20/7/2021	Cohort	At least one dose of Comirnaty or Spikevax	Kaiser Permanente (healthcare provider) Southern California members	Myocarditis	8 (Comirnaty) 7 (Spikevax)	18-40 years	100%	13 cases occurred following second dose
Starekova et al. **(35)**	1/1/2021 – 25/5/2021	Retrospective review of medical records	Comirnaty or Spikevax (2 doses)	Admissions to University of Wisconsin hospital	Myocarditis	5	17-38 years	80%	2

NR = Not Reported
*71% of all reports following a second vaccine dose involved Comirnaty

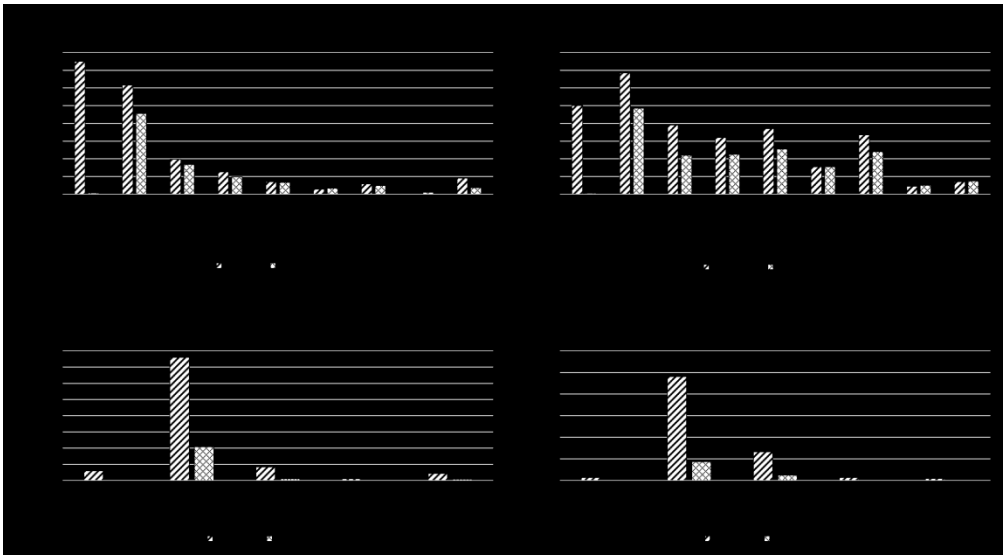

Figure 1: Histogram of the age of vaccinees reporting to VAERS and EudraVigilance. (A) Reports of myocarditis to VAERS; (B) Reports of pericarditis to VAERS; (C) Reports of myocarditis to EudraVigilance; (D) Reports of pericarditis to EudraVigilance.

447x246mm (236 x 236 DPI)

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2 (see separate checklist for detail)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5/6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5/6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5/6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5/6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5/6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A (descriptive)
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	6-9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	Table 5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8-9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A Results presented in Table 5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9-10
	23b	Discuss any limitations of the evidence included in the review.	11
	23c	Discuss any limitations of the review processes used.	11
	23d	Discuss implications of the results for practice, policy, and future research.	11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	13
Competing interests	26	Declare any competing interests of review authors.	13

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	13-14

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3 & 4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	n/a – all patients spontaneously reporting events of myocarditis and pericarditis were included
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and	4 (confounders and effect modifiers not applicable)

		effect modifiers. Give diagnostic criteria, if applicable	
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	4
Bias	#9	Describe any efforts to address potential sources of bias	n/a – not possible to address bias in spontaneously reported data. Biases discussed as a limitation on page 8
Study size	#10	Explain how the study size was arrived at	n/a – all spontaneously reported events of myocarditis and pericarditis to the UK's Yellow Card scheme, US VAERS, and EEA EudraVigilance were included
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	n/a – not applicable in this study

Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	n/a – no statistical methods were applied
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	n/a – not applicable for the data used
Statistical methods	#12c	Explain how missing data were addressed	n/a – not applicable for these datasets; missing information within spontaneous reports mentioned as a limitation on page 8
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a – no analytical statistical methods applied; no sampling
Statistical methods	#12e	Describe any sensitivity analyses	n/a – no sensitivity analyses conducted
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	5 & 6; Tables 1, 2, 3a, 3b & 4

Participants	#13b	Give reasons for non-participation at each stage	n/a – all patients reporting myocarditis and pericarditis to spontaneous reporting systems of UK, US and EEA were included up to the datalock point
Participants	#13c	Consider use of a flow diagram	n/a
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	5 & 6; All tables
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	Tables 2-4
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	5 & 6; Tables 1-4
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	n/a – only descriptive statistics (counts and percentages) used

		confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	Tables 2-4
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a – not appropriate for these data as no comparator
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	5 & 6
Discussion			
Key results	#18	Summarise key results with reference to study objectives	6 & 7
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	7 & 8
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	7 - 9

Generalisability	#21	Discuss the generalisability (external validity) of the study results	9
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

BMJ Open

Reports of myocarditis and pericarditis following mRNA COVID-19 vaccines: A systematic review of spontaneously reported data from the UK, Europe, and the US and of the literature

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Keywords:	COVID-19, Adverse events < THERAPEUTICS, PUBLIC HEALTH

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Reports of myocarditis and pericarditis following mRNA COVID-19 vaccines: A systematic review of spontaneously reported data from the UK, Europe, and the US and of the literature

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Word count: (excluding tables): 4647

Number of tables: 6

Number of figures: 4

Abstract

Objectives: To bring together spontaneously reported data from multiple countries to estimate reporting rate, and better understand risk factors for myocarditis and pericarditis following COVID-19 mRNA vaccines.

Design: Systematic review of spontaneously reported data from United Kingdom (UK), United States (US), and European Union/European Economic Area (EU/EEA) and of the literature.

Data sources: UK Yellow Card scheme, Vaccine Adverse Event Reporting System (VAERS), EudraVigilance were searched from date of vaccine launch to 14-16 March 2022. PubMed/MEDLINE and Embase were searched to 15 March 2022.

Eligibility criteria: We included publicly available spontaneous reporting data for "Myocarditis" and "Pericarditis" from UK, US, and EU/EEA following COVID-19 mRNA vaccines. Pharmacoepidemiological observational studies investigating myocarditis/pericarditis following mRNA COVID-19 vaccines were included (no restrictions on language or date). Critical Appraisal Skills Programme (CASP) tools assessed study quality.

Data extraction and synthesis: Two researchers extracted data. Spontaneously reported events of myocarditis and pericarditis were presented for each data source, stratified by vaccine, age, sex, and dose (where available). Reporting rates were calculated for myocarditis and pericarditis for each population. For published pharmacoepidemiological studies, design, participant characteristics, and study results were tabulated.

Results: Overall, 18,204 myocarditis and pericarditis events have been submitted to the UK, US, and EU/EEA regulators during the study period. Males represented 62.24% (n=11,331) of myocarditis and pericarditis reports. Most reports concerned vaccinees aged <40 years and were more frequent following a second dose. Reporting rates were consistent between the data sources. Thirty-two pharmacoepidemiological studies were included; results were consistent with our spontaneous report analyses.

Conclusions: Younger vaccinees more frequently report myocarditis and pericarditis following mRNA COVID-19 vaccines than older vaccinees. Results from published literature supported the results of our analyses.

Strengths and Limitations of the Study

- This is the first study to bring together spontaneously reported data from the United Kingdom, United States, and Europe on myocarditis and pericarditis following mRNA COVID-19 vaccines.
- Results from this study provide evidence on the frequency of reported events of myocarditis and pericarditis following mRNA vaccines in different age groups, and by sex and vaccine dose; analyses of spontaneous reports were consolidated with results of published literature, identified by systematic review.
- Results may have been influenced by biases including different vaccination policies in each region examined, and publicity on events of myocarditis and pericarditis following mRNA vaccines.
- The study relied on outputs from spontaneous reporting systems in which the level of detail differed between the systems examined; furthermore, it is not possible to estimate incidence

rates using spontaneous reports due to the lack of data on the exposed population, and there is no unvaccinated comparison group.

- There is an urgent need for further pharmacoepidemiological studies to be conducted to provide more accurate estimates of the frequency, clinical course, long term outcome, effects of treatment and impact on quality of life, to address many of the limitations of spontaneous reporting.

1.0 Introduction

Messenger RNA (mRNA) based vaccines have been extensively used world-wide in the fight against COVID19 that continues to pose a threat, with many countries initiating booster campaigns, yet these are the first in their class of vaccines to be approved for use, and as such continued monitoring of their safety is required. In the 15 months since first approval mRNA-based vaccines have had several adverse reactions documented, including myocarditis and pericarditis. Signals of myocarditis and pericarditis were first identified in Israel where there had been 148 cases of myocarditis reported within 30 days of vaccination, with the majority of these cases (n=121) reported after the second dose (1). Since the emergence of this signal, multiple countries have reported myocarditis and pericarditis following mRNA COVID-19 vaccines (2) and these events have been listed in the product information for both Pfizer-BioNTech (Comirnaty) and Moderna (Spikevax) mRNA COVID-19 vaccines (3-9). The identification of this safety signal early in the vaccination programme indicated that young males were at higher risk of developing myocarditis or pericarditis, particularly after the second dose of either mRNA based COVID-19 vaccine (2, 10-12). Myocarditis and pericarditis events following COVID-19 mRNA vaccines occur very rarely at a frequency of 10-20 events per 100,000 (13, 14), and the clinical course is typically mild with most cases making a full recovery (15).

Vaccination programmes around the world have differed in their roll-out and vaccine type used, with a general pattern that those most at risk of severe COVID-19 complications were prioritised for vaccination, followed by healthy adults and then children; in all these groups mRNA vaccines have been approved and used alongside adenovirus vector vaccines and inactivated virus vaccines around the world (4-9, 16, 17). Waves of COVID-19 infections in different countries also altered the speed of vaccine roll-out and the time interval between vaccine doses, thus interpretation of the data from several countries may reveal risk factors for myocarditis and pericarditis following exposure to COVID-19 mRNA vaccines. Here we collate spontaneous reports of myocarditis and pericarditis following COVID-19 vaccination, with a systematic review of the literature, to capture and interpret the evidence to date.

2.0 Materials and Methods

The data sources were spontaneous reporting system outputs of the UK Yellow Card scheme, the US Vaccine Adverse Event Reporting System (VAERS) via the CDC Wonder online tool, and the EU/EEA EudraVigilance system were used to estimate the frequency of reported cases of myocarditis and pericarditis following COVID-19 Vaccine Pfizer/BioNTech (Comirnaty) and COVID-19 Vaccine Moderna (Spikevax) (18-20). These systems collect unsolicited suspected adverse events to vaccines and medications from healthcare professionals and consumers. The process of spontaneous reporting requires suspected association with the mRNA vaccine to the event by the reporting individual. For reports following a mRNA COVID-19 vaccine, all reports coded “myocarditis” and “pericarditis” which had been spontaneously reported to these systems between the date of vaccine launch and the datalock point were counted. Cases were stratified by age, sex, and vaccine dose where these data were available.

The datalock point (defined as the date that searches were ran in the database) was 14 March 2022 for VAERS and EudraVigilance, and 16 March 2022 for the Yellow Card scheme. Data from the Yellow Card scheme is released weekly, with data up to 16 March 2022 the closest release to the 14 March 2022 datalock point used for VAERS and EudraVigilance.

The number of vaccinated individuals per vaccine brand in the UK, US, and EU/EEA were obtained from the websites of the MHRA, the CDC in the US, and the European Centre for Disease Prevention and Control (ECDC) up to the date closest to the datalock point for ADR spontaneous reports (11, 21, 22). Reporting rates of myocarditis and pericarditis per million vaccines administered were calculated for those who had received at least one dose of each vaccine brand.

2.1 Literature Review

A systematic literature review was conducted using PubMed/Medline and Embase literature databases. No review protocol was prepared.

The datalock point was 15 March 2022. Studies were included if they were observational in design (excluding case reports and case series), and involved at least one patient who experienced myocarditis, pericarditis, or myopericarditis following any mRNA COVID-19 vaccine (any case definition was accepted). Pre-print manuscripts were included if no peer-reviewed version was available. Studies of other designs and studies investigating other vaccines were excluded. Studies investigating cardiac effects of SARS-CoV-2 infection were excluded. No restrictions on language or date were applied.

The search terms used were:

(myocarditis OR pericarditis OR myopericarditis) AND (covid-19) AND (vaccine)

Data were extracted for study design, study period, vaccine of interest, population, number of cases of myocarditis or pericarditis, and where specified the percentage of cases who were male, age, and the vaccine dose after which the event occurred. Two reviewers extracted data. These data were tabulated.

Study quality was assessed by two reviewers, using the relevant Critical Appraisal Skills Programme (CASP) tool (available on request) (23). Each checklist covers a different study design and contains a series of questions to critically appraise the research.

2.2 Patient and Public Involvement

Patients and the public were not consulted during this study.

3.0 Results

3.1 Systematic review of the literature identified thirty-two observational studies

In order to collate information specific to address the issue identification of characteristics of myocarditis and pericarditis following COIVD-19 mRNA vaccines a detailed review of the literature was carried out, using the search terms specified in the materials of methods (Section 2.1). Initially 702 records were identified, following de-duplication, assessment for eligibility and quality 32 studies were included in our analysis (Figure 1). The information extracted in these studies has been assessed alongside the evidence from spontaneous reporting systems, below.

3.2 Myocarditis and Pericarditis occur very rarely following COVID-19 mRNA vaccines

Overall, across the three spontaneous reporting databases examined covering the UK, US, and EU/EEA populations, there were a total of 18,204 events of myocarditis and pericarditis submitted to the regulators.

From the UK's MHRA Yellow Card scheme, 1260 reports were following Comirnaty administration, and 325 reports were following Spikevax (Table 1; Figure 2A). As of 16 March 2022, it was estimated that 26.2 million first doses and 23.6 million second doses of Comirnaty had been administered in the UK (11). Therefore, there were approximately 48.09 cases of myocarditis and pericarditis per million vaccinees who had received at least one dose of Comirnaty (Figure 2B). To the same date, approximately 1.6 million first doses and 1.5 million second doses of Spikevax had also been administered (11). Of those who had received at least one dose of Spikevax in the UK, 203.13 cases of myocarditis and pericarditis had been reported per million vaccinated (Figure 2B).

The US VAERS system contains 2986 reported events following Comirnaty and 1640 events following Spikevax (Table 2; Figure 2A). In the US, there had been 124.12 million vaccinees who had been fully vaccinated with Comirnaty (21) giving a reporting rate of 14.70 cases of myocarditis and 9.36 cases of pericarditis per million fully vaccinated individuals, combined to 12.03 cases of myocarditis and pericarditis per million fully vaccinated with Comirnaty (Figure 2B). There had been 75.57 million people fully vaccinated with Spikevax (21) therefore there were 12.35 cases of myocarditis reported per million fully vaccinated Spikevax recipients and 9.36 cases of pericarditis per million fully vaccinated Spikevax recipients, combined giving a reporting rate of both myocarditis and pericarditis as 10.86 per million Spikevax vaccinees (Figure 2B).

The EudraVigilance database contained the highest total reports of events with 9211 events reported following Comirnaty and 2786 following Spikevax (Table 3; Figure 2A). There had been approximately 296.05 million vaccinees who had received at least one dose of Comirnaty in the EU/EEA (22). Therefore, the reporting rates were calculated as 14.50 reports of myocarditis and 16.61 reports of pericarditis per million Comirnaty recipients, giving a combined reporting rate of 15.56 cases of myocarditis and pericarditis per million people who received at least one dose of Comirnaty (Figure 2B). For Spikevax, there had been approximately 46.56 million first doses of Spikevax administered in the EU and EEA (22). Thus, reporting rates in the EU/EEA are currently 28.01 reports of myocarditis and 31.83 reports of pericarditis per million vaccinees, giving a combined reporting rate of 29.92 per million Spikevax recipients (Figure 2B).

In total, there were 13,573 events of myocarditis and/or pericarditis reported in the observational studies identified by systematic review of the literature.

While reporting rates for myocarditis and pericarditis have differed between the spontaneous reporting databases, overall, they demonstrate that these events are very rare (defined as occurring at a rate of <1 in 10,000) (24).

3.3 Fatalities following myocarditis and pericarditis after COVID-19 mRNA vaccines

There have been cases of myocarditis and pericarditis with a fatal outcome reported to spontaneous reporting systems and in the literature. There were four fatalities in the UK (0.25% of all spontaneous reports), 62 in the US (1.3% of all reports) and 56 in the EU/EEA (0.6% of all reports). Where age of fatal cases was reported (EudraVigilance and VAERS databases only), 85.83% (n=103) of fatal cases overall were aged 18 years or older. Five cases (4.17%) were aged under 18 years; all were myocarditis

events (6.41% of all fatal myocarditis events reported). Ten percent of fatal cases had age unspecified. All fatal cases of pericarditis reported to EudraVigilance and VAERS were aged 18 years or older.

Fatal cases were reported in five of the 32 included studies identified by systematic literature review (Table 4) (25-29). Overall, 0.22% (n=30) of 13,571 myocarditis or pericarditis events reported in the literature had a fatal outcome (range 0.41-45.85%; Table 4). Characteristics of fatal cases were specified in one study (25). In this study, results indicated that fatal cases of myocarditis and pericarditis occurred in the adult population. There were 15 fatal myocarditis events (median age 60 [Interquartile Range (IQR) 56-78] years), 5 fatal pericarditis events (median age 71 [IQR 67-77] years), and two fatal myopericarditis events (aged 55 and 83 years).

3.4 Young males are more likely to suffer myocarditis and pericarditis following COVID-19 mRNA vaccination

To confirm the early evidence that young males were most susceptible to the adverse reaction of myocarditis and pericarditis (1), we compared spontaneous reporting and the literature up until 16 March 2022 to determine whether this signal has been maintained since initially identified. Of the myocarditis and pericarditis events reported to the Yellow Card scheme, 60.92% were from males with a trend towards increased frequency in younger age groups (Table 1; Figure 3A). This trend of more frequent reporting from males was similar across the three regions assessed, with 72.92% in the US and 60.75% in the EU/EEA (Figure 3A), as well as similar reporting trends between the vaccine types (Figure 3B).

Most reports of myocarditis in the US were from vaccinees aged 18-39 years (n=1303, 47.3% of 2757 reports), while in the EU 79.2% (n=4431) of reports of myocarditis where from people aged 18-64 years (Table 3). In the US, 59.39% of pericarditis events were reported from males (Table 2) and the age distribution of those who reported pericarditis was wide, covering many age categories (Table 2). In the EU, 50.43% of the reported pericarditis events occurred in males (Table 3). The trend in age was less distinct, with children (3-11 years) and the elderly (aged older than 85 years) populations accounting for 35.7% and 43.97% of reported cases, respectively (Table 3).

Analysis of the literature determined that on average 60.31% of myocarditis and/or pericarditis events following COVID-19 mRNA vaccines occurred in males (range 50.00-100.00%). Results of these studies indicate that the incidence for myocarditis and pericarditis was higher for males than for females. Due to differences in study design it was not possible to determine the age group most susceptible to myocarditis and pericarditis from the literature as some studies were focused on adults only or children only meaning appropriate comparisons could not be carried out.

3.5 Most myocarditis and pericarditis events are reported following the second mRNA vaccine dose

Analysis of data following booster programme roll out has enabled detailed analysis into the frequency of reports following each dose of a COVID-19 mRNA vaccine. Data for the US is stratified by dose and demonstrates that the majority of reported myocarditis and pericarditis events occurred following the second dose (Figures 4A, 4B). For Comirnaty, of the total 1824 myocarditis events reported to VAERS, 956 (52.41%) followed the second dose, while 383 (21.00%) were reported after a single dose of the vaccine (Table 5a). Similarly, 45.78% of pericarditis events were reported to VAERS following two doses of Comirnaty (n=532 of 1162 reported events where vaccine dose was specified; Table 5a). For Spikevax, 384 of 933 (41.16%) reported events of myocarditis and 305 of the 707 (43.14%) reported

events of pericarditis occurred following two doses of the vaccine (Table 5b). Approximately 10% of myocarditis and pericarditis events had been reported following a third dose for both vaccines up to 14 March 2022 (Tables 5a and 5b).

This data is in agreement with other studies where 64.72% (range 25.00% and 91.78%) of myocarditis and pericarditis events occurred following the second vaccine dose (Table 4).

4.0 Discussion

There have been a small number of reports of myocarditis and pericarditis following exposure to mRNA COVID-19 vaccines in each database examined, considering the number of people who have received a COVID-19 vaccine in each region. In all spontaneous reporting systems and for both mRNA vaccines, the reporting rate of myocarditis was higher than that of pericarditis. This may be true, or it may also reflect that the diagnosis of myocarditis is relatively more straightforward. In the UK and EU/EEA, reporting rates of myocarditis and pericarditis were higher following Spikevax compared with those for Comirnaty. However, this was not observed for the US. A full dose of Spikevax used for first and second doses contains 100 micrograms of mRNA nucleotides, whereas a full dose of Comirnaty contains 30 micrograms of the mRNA material (4, 5). This is one possible reason for the higher reporting rate of myocarditis and pericarditis observed for Spikevax in the UK population. A half-dose of Spikevax is used for booster vaccination doses; this still contains more genetic material than Comirnaty (4). Therefore, it will become increasingly important as more people receive third and subsequent booster doses of mRNA COVID-19 vaccines to monitor the frequency and severity of myocarditis and pericarditis following exposure to these vaccines.

The UK had the highest reporting rate for both myocarditis and pericarditis following mRNA vaccines, particularly for events following Spikevax. Reporting rates from the UK showed higher variability compared with those of the US and EU/EEA; reporting rates were higher for myocarditis and pericarditis following Spikevax in the UK, compared to EU/EEA and US reporting rates and incidence reported in the literature. This variability is potentially due to the fact that the UK MHRA Yellow Card scheme had the lowest number of spontaneous reports (Figure 1A) as well as the lowest vaccination coverage for Spikevax leading to uncertainty and variability. Analysis of multiple sources was thus essential to provide accurate reporting rates. It is possible that the UK and EU/EEA have stronger spontaneous reporting systems compared with the US, which may explain the higher reporting rates observed for this population. The frequency of events noted by regulators, the World Health Organisation, and in the vaccines' summaries of product characteristics (SmPC) suggest that myocarditis and pericarditis are very rare, occurring in less than one in 10,000 vaccine doses administered (2, 6, 7, 10, 11). Our calculated reporting rates for myocarditis and pericarditis following mRNA vaccines in each of the UK, US, and EU/EEA were consistent with this. However, underreporting of the events to regulators is possible, therefore it may be that the events of myocarditis and pericarditis are 'rare' events (more frequent than 1/10,000) rather than 'very rare' (less frequent than 1/10,000) events as suggested. Conversely greater reporting may have occurred due to the public interest in adverse reactions linked with COVID-19 vaccines, thus analysis of multiple data sources was used here to overcome these potential limitations. In October 2021, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency announced a plan to review the risk of myocarditis and pericarditis following mRNA vaccines (30). It is therefore possible that updates to the vaccines' SmPC will be required once this review is complete.

When examining the demographics of vaccinees who had reported myocarditis or pericarditis following mRNA vaccines, both events appear to more commonly affect males compared with females, particularly amongst vaccinees of younger age categories (Tables 2, 3, 5a, 5b). This is consistent with early reports surrounding these events, where it was suggested that younger males appear at higher risk of myocarditis and pericarditis following mRNA vaccines (1). Demographic data was available for VAERS and EudraVigilance populations separated by myocarditis and pericarditis; in these databases results were similar with more than 70% of myocarditis and more than 50% of pericarditis events reported in males (Tables 2 and 3). These results are consistent with results of pharmacoepidemiological studies in the published literature; in the studies where sex was reported, more than 60% of patients were male (Table 6) (31-36). This is an interesting finding, as it has been previously suggested that over 70% of reports to VAERS involve females (32). It is possible that the event was missed or misclassification occurred in older adults, particularly in older individuals in the three populations of interest who were vaccinated prior to the signal emerging. It is also possible that some of the symptoms of myocarditis and pericarditis, for example chest pain and breathlessness, were attributed to other cardio-respiratory conditions in older people. Nonetheless, it is known that most cases of myocarditis (any cause) occur in young adults, with males more commonly affected than females; this supports the results observed in this study (37, 38). Alternatively, vaccine roll-out in each of the regions may have affected the results observed in some of the countries, including availability of different vaccines and corresponding age distributions of those receiving each vaccine in different regions; for instance in the UK, mRNA vaccines were more frequently used in younger age groups, while older vaccinees may have been more likely to receive an adenovirus vector vaccine.

We appreciate that there will be regional differences in COVID-19 strains as well as endemic viruses circulating in the populations, and these may have been the underlying cause of myocarditis and pericarditis in the reporting populations examined. However, it is not possible to identify or quantify these in spontaneously reported data. In order to overcome these differences, we have analysed data from three different spontaneous reporting systems and worldwide data from the literature to identify trends in this very rare event. As this is a very rare event with small numbers of people affected, it is important to bring together data from around the world to identify trends that may not be seen within one population. Further analysis is required in discrete populations, if appropriate, to better stratify patients, aiding classification of groups according to risk factors for adverse events following vaccination.

Data on vaccine dose were only available from the VAERS database. Most cases reported to VAERS followed a second dose of vaccine (Tables 5a and 5b). This is consistent with the early signal which emerged in Israel, where 121 of the 148 reported cases of myocarditis occurred around the time of the second dose of COVID-19 vaccine (1). Furthermore, similar results were observed by Hajjo et al., who found only a very small number of events occurring after a third dose in their analysis of VAERS data (39).

Pharmacoepidemiological studies identified by systematic review (Table 6) were consistent with results found in spontaneously data from VAERS and EudraVigilance (Tables 2-3, 5a-6). Young males more frequently reported myocarditis in each of these studies and found in our analysis of spontaneous reporting data. Furthermore, reports were more frequent following a second dose of mRNA vaccine, although time intervals between doses was not specified and may also differ between regions. Therefore incorporation of the evidence on dosing effects from the VAERS system and the literature indicated that following the second dose was when the most myocarditis and pericarditis events occurred. Continuous monitoring of this will be required, especially following subsequent doses of mRNA vaccines.

Myocarditis has been observed historically following vaccination, including after smallpox, influenza, and hepatitis B vaccines; prior to COVID-19 0.1% of reports to VAERS between 1990 and 2018 had been in relation to myopericarditis (13). Furthermore, myocarditis is known to occur after a range of viral infections, including coronaviruses which cause Middle East Respiratory Syndrome (MERS) and COVID-19, with viral infection the most common cause of myocarditis (40-42). This study provides evidence that younger vaccinees more frequently report myocarditis and pericarditis following mRNA COVID-19 vaccines compared with older vaccinees, and reports are more frequent following the second dose. Results were consistent between each of the three data sources used. This is an important finding, because as vaccination programmes around the world progress, rates of myocarditis and pericarditis are likely to increase. The effect of booster vaccinations with mRNA COVID-19 vaccines on the development of myocarditis and pericarditis is largely unknown. Furthermore, mRNA COVID-19 vaccines (particularly Spikevax) are being supplied to the COVAX initiative for distribution throughout low- and middle-income countries, where diagnostic imaging and access to healthcare is more difficult (43, 44). Regulatory authorities should continue to monitor the effects that mRNA vaccination might have on the heart in the populations for which they are responsible. The proportions of young people are higher in low- and middle-income countries' populations compared to high income countries. Issuing diagnostic criteria and treatment protocols for myocarditis and pericarditis with mRNA COVID-19 vaccines that take into consideration the capabilities of the local healthcare system are also important.

4.1 Limitations

Vaccination policies in the three regions may have biased the results towards a higher number of adverse events reports myocarditis and pericarditis from younger vaccinees compared with older vaccinees. In each of these regions, younger people were more likely to have received mRNA vaccines, which may have contributed to higher reporting rates of myocarditis and pericarditis in younger vaccinees. The frequency of reported events per age group was presented as a crude number, and reporting rates could only be calculated as an overall estimate rather than stratified by age; based on the data available for vaccinations administered, it was not possible to determine the proportion of all vaccinees per age group who reported an event of myocarditis or pericarditis. This is very important, because it is likely that the reporting rate of myocarditis and pericarditis with mRNA COVID-19 vaccines will be higher in young people and even higher in young men if the reporting rates are stratified by age and sex. The regulatory authorities and Marketing Authorisations Holders (MAHs) need to follow up reports of these conditions with reporters to obtain as much information and make this information available publicly. Myocarditis and pericarditis following mRNA COVID-19 vaccines is an area which requires further research.

The data sources for this study were spontaneous reporting systems of the UK, US, and EEA. All spontaneous reporting systems have well-known limitations including missing information, and reporting bias caused by publicity surrounding a particular adverse event (45). Misclassification of myocarditis and pericarditis, or differing definitions of these events between the regions analysed, is also possible particularly before these events attracted publicity or among older age groups. The definition and diagnosis of "Myocarditis" and "Pericarditis" are based on the reporters' statements, and are not usually validated by the regulatory authority receiving the report. Under-reporting is a major limitation of spontaneous reporting; even with the intense publicity and global attention on COVID-19 vaccine safety, it is possible that not all cases are reported to regulatory authorities (46, 47). Furthermore, a report to spontaneous reporting systems indicates suspicion that the event was associated with the vaccine, it does not confirm that the vaccine caused the event (11, 45). Further

assessment is required to determine causality for each report. Finally, it is not possible to estimate incidence rates using spontaneous reports, and there is no unvaccinated comparison group (45).

Using publicly available data introduced some challenges, as the level of detail available was limited and varied between data sources. Data on the vaccine dose on which the reported events of myocarditis and pericarditis occurred were only available for the US VAERS population. Information contained within individual reports is not routinely made available, however these comprise important clinical information that would allow better understanding of each case. Such details should be made publicly available. Better transparency is needed to allow more robust research using spontaneous reporting to be undertaken.

Due to the limited published research into myocarditis and pericarditis following mRNA COVID-19 vaccines, we included all pharmacoepidemiological study designs (except case reports and case series) and considered all study populations and all study periods for inclusion. The purpose of systematically reviewing the literature was to determine whether results from our analyses of spontaneous reports were consistent with other evidence currently available. Due to the short time period since vaccine programmes were initiated and the heterogenous nature (regional differences, age, sex, and disease status of participants) of the included studies, no pooling of data, syntheses, or meta-analyses could be completed. It should be noted that there were no formal assessments of publication bias during the systematic literature review. However, a CASP checklist was completed for each included study, which deemed the research to be of sufficient quality for inclusion. Nonetheless, each study had limitations which should be considered when interpreting their results. The possibility of publication bias was not formally analysed.

Further pharmacoepidemiological studies are urgently needed to address many of the limitations of spontaneous reporting in understanding myocarditis and pericarditis following mRNA COVID-19 vaccines including more accurate estimates of the frequency, better understanding of the clinical course and the effects of these events on quality of life. It is also important to compare the incidence and characteristics of these events with recipients of other non-mRNA COVID-19 vaccines and unvaccinated people. However, these studies will take time to be conducted.

5.0 Conclusions

This study adds to existing evidence that younger vaccinees more frequently report myocarditis and pericarditis following mRNA COVID-19 vaccines compared with older vaccinees, and reports are more frequent following the second dose. These events are very rare or possibly rare according to the estimated reporting rates from spontaneous adverse reactions. The events were more frequently reported amongst males, and most reports came from vaccinees aged under 30 years. The clinical course of these events is typically mild, with full recovery in most cases.

The study brings together spontaneously reported adverse event data from three regions. Consistencies in the reporting rates and trends of myocarditis and pericarditis within the three data sources utilised suggest that results may be generalisable to other populations in which mRNA vaccines are used. However, limitations of the data sources used and biases which may have affected results should be considered. It is important that regulatory authorities continue to monitor the effects of mRNA vaccines on the heart, particularly as vaccine programmes progress to include younger vaccinees in many parts of the world. Myocarditis and pericarditis following mRNA COVID-19 vaccines is an area which requires further research, especially in children and adolescents and following third and subsequent (booster) doses. Pharmacoepidemiological studies are urgently needed to address many of the limitations of spontaneous reporting in understanding myocarditis and

pericarditis following mRNA COVID-19 vaccines including more accurate estimates of frequency, a better understanding of the clinical course, and the effects on quality of life. However, they will take time to be conducted. We believe that the data we describe here will enhance the understanding of these conditions and help with identification of potential sources of mechanisms of vaccine-associated myocarditis and pericarditis by identifying which populations are most likely to suffer these adverse events following COVID-19 mRNA vaccination.

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7.0 Figure Legends

Figure 1: Flowchart detailing inclusion of studies for systematic review

Literature searches were carried out in PubMed/MEDLINE and simultaneously in Embase. The identified records were de-duplicated prior to screening to remove duplicate publications. Records were then screened to remove literature that did not meet the search criteria and eligibility was assessed prior to inclusion into the literature review.

Figure 2: Event counts and reporting rates of myocarditis and pericarditis in the UK, US and EU

(A) Events of myocarditis and pericarditis reported to the Yellow Card scheme (UK), VAERS (US) and EudraVigilance (EU) reporting systems following any dose of COVID-19 mRNA vaccines separated by vaccine manufacturer combined to give total counts. (B) Reporting rates of myocarditis and pericarditis following any dose of COVID-19 mRNA vaccine separated by vaccine manufacturer and reporting region.

Figure 3: Myocarditis and pericarditis reports separated by gender

(A) Percentage of males and females experiencing myocarditis and pericarditis reported to each reporting system (Yellow Card, VAERS and EudraVigilance). Bars represent the total of all myocarditis and pericarditis reports to each system, separated by gender, where bars do not meet 100% indicates reports where gender was not specified. Values indicate the percentage of males experiencing these events. (B) Reports in each region were stratified by vaccine manufacturer as well as gender experiencing these events. Stacked bars represent the total number of reports, where gender was specified, from each region for each vaccine type. Values depict the percentage of males that experienced these events.

Figure 4: Myocarditis and pericarditis events following COVID-19 mRNA vaccination separated by dose

Data from the VAERS (US) reporting system was separated by reaction type; myocarditis (A) and pericarditis (B), vaccine manufacturer and by dose received. Stacked bars represent the male and female reports of each condition according to the dose received.

Table 1: Reports of myocarditis and pericarditis submitted to Yellow Card scheme, by age and sex. Datalock point 16 March 2022.

	Comirnaty		Spikevax		Total	
	n	%	n	%	n	%
Age group (years						
<18 Years	70	5.68	0	0.00	70	4.50
18-29 Years	372	30.19	114	35.19	486	31.23
30-39 Years	299	24.27	92	28.40	391	25.13
40-49 Years	137	11.12	48	14.81	185	11.89
50-59 Years	92	7.47	22	6.79	114	7.33
60+ Years	146	11.85	15	4.63	161	10.35
Age not specified	144	11.69	34	10.49	178	11.44
Sex						
Female	492	39.94	109	33.64	601	38.62
Male	731	59.33	206	63.58	937	60.22
Sex not specified	37	3.00	10	3.09	47	3.02
Total	1260	100.00	325	100.00	**1585**	**100.00**

Table 2: Myocarditis and pericarditis events reported to VAERS overall. Datalock point 14 March 2022. Percentages per age group are presented.

Age Group	Myocarditis								Pericarditis							
	Male		Female		Sex Not Specified		Total		Male		Female		Sex Not Specified		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	N	%
Comirnaty (PfizerBioNTech)																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.23	0	0.00	1	0.09
3-5 Years	2	0.15	0	0.00	0	0.00	2	0.11	1	0.14	0	0.00	0	0.00	1	0.09
6-17 Years	525	38.80	67	15.44	2	5.41	594	32.57	145	20.14	23	5.32	1	10.00	169	14.54
18-29 Years	404	29.86	102	23.50	1	2.70	507	27.80	217	30.14	51	11.81	0	0.00	268	23.06
30-39 Years	157	11.60	69	15.90	2	5.41	228	12.50	116	16.11	78	18.06	0	0.00	194	16.70
40-49 Years	68	5.03	59	13.59	0	0.00	127	6.96	56	7.78	83	19.21	0	0.00	139	11.96
50-59 Years	41	3.03	56	12.90	0	0.00	97	5.32	64	8.89	73	16.90	0	0.00	137	11.79
60-64 Years	13	0.96	21	4.84	2	5.41	36	1.97	20	2.78	43	9.95	0	0.00	63	5.42
65-79 Years	52	3.84	31	7.14	2	5.41	85	4.66	67	9.31	50	11.57	2	20.00	119	10.24
80+ Years	5	0.37	4	0.92	0	0.00	9	0.49	12	1.67	9	2.08	0	0.00	21	1.81
Not Specified	86	6.36	25	5.76	28	75.68	139	7.62	22	3.06	21	4.86	7	70.00	50	4.30
Total	1353	100.00	434	100.00	37	100.00	**1824**	100.00	720	100.00	432	100.00	10	100.00	**1162**	100.00
Spikevax (Moderna)																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	5	0.78	1	0.37	2	10.53	8	0.86	1	0.26	0	0.00	0	0.00	1	0.14
18-29 Years	317	49.15	64	23.79	1	5.26	382	40.94	130	33.33	62	20.39	0	0.00	192	27.16
30-39 Years	135	20.93	51	18.96	0	0.00	186	19.94	59	15.13	38	12.50	1	7.69	98	13.86
40-49 Years	62	9.61	51	18.96	0	0.00	113	12.11	57	14.62	54	17.76	0	0.00	111	15.70
50-59 Years	41	6.36	37	13.75	1	5.26	79	8.47	52	13.33	52	17.11	0	0.00	104	14.71

60-64 Years	15	2.33	24	8.92	0	0.00	39	4.18	24	6.15	31	10.20	1	7.69	56	7.92
65-79 Years	29	4.50	35	13.01	0	0.00	64	6.86	54	13.85	53	17.43	2	15.38	109	15.42
80+ Years	5	0.78	4	1.49	0	0.00	9	0.96	6	1.54	11	3.62	0	0.00	17	2.40
Not Specified	36	5.58	2	0.74	15	78.95	53	5.68	7	1.79	3	0.99	9	69.23	19	2.69
Total	645	100.00	269	100.00	19	100.00	**933**	100.00	390	100.00	304	100.00	13	100.00	**707**	100.00
Overall (both mRNA vaccines)																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.14	0	0.00	1	0.05
3-5 Years	2	0.10	0	0.00	0	0.00	2	0.07	1	0.09	0	0.00	0	0.00	1	0.05
6-17 Years	530	26.53	68	9.67	4	7.14	602	21.84	146	13.15	23	3.13	1	4.35	170	9.10
18-29 Years	721	36.09	166	23.61	2	3.57	889	32.25	347	31.26	113	15.35	0	0.00	460	24.61
30-39 Years	292	14.61	120	17.07	2	3.57	414	15.02	175	15.77	116	15.76	1	4.35	292	15.62
40-49 Years	130	6.51	110	15.65	0	0.00	240	8.71	113	10.18	137	18.61	0	0.00	250	13.38
50-59 Years	82	4.10	93	13.23	1	1.79	176	6.38	116	10.45	125	16.98	0	0.00	241	12.89
60-64 Years	28	1.40	45	6.40	2	3.57	75	2.72	44	3.96	74	10.05	1	4.35	119	6.37
65-79 Years	81	4.05	66	9.39	2	3.57	149	5.40	121	10.90	103	13.99	4	17.39	228	12.20
80+ Years	10	0.50	8	1.14	0	0.00	18	0.65	18	1.62	20	2.72	0	0.00	38	2.03
Not Specified	122	6.11	27	3.84	43	76.79	192	6.96	29	2.61	24	3.26	16	69.57	69	3.69
Total	1998	100.00	703	100.00	56	100.00	2757	100.00	1110	100.00	736	100.00	23	100.00	1869	100.00
Grand Total	**1998**	**72.47**	**703**	**25.50**	**56**	**2.03**	**2757**	**100.00**	**1110**	**59.39**	**736**	**39.38**	**23**	**1.23**	**1869**	**100.00**

Table 3: Myocarditis and pericarditis events reported to EudraVigilance for the European Economic Area. Datalock point 14 March 2022. Percentages per age group are presented.

Age Group	Myocarditis								Pericarditis							
	Male		Female		Sex Not Specified		Total		Male		Female		Sex Not Specified		Total	
	n	%	n	%	n	%	N	%	n	%	n	%	n	%	N	%
Comirnaty (Pfizer/BioNTech)																
2 Months-2 Years	0	0.00	0	0.00	0	0.00	0	0.00	67	63.81	38	36.19	0	0.00	105	100.00
3-11 Years	4	66.67	2	33.33	0	0.00	6	100.00	798	48.33	848	51.36	5	0.30	1651	100.00
12-17 Years	507	86.82	72	12.33	5	0.86	584	100.00	164	56.75	125	43.25	0	0.00	289	100.00
18-64 Years	2302	70.16	956	29.14	23	0.70	3281	100.00	307	46.30	351	52.94	5	0.75	663	100.00
65-85 Years	130	50.58	125	48.64	2	0.78	257	100.00	54	46.55	62	53.45	0	0.00	116	100.00
85+ Years	12	52.17	11	47.83	0	0.00	23	100.00	1042	50.27	1026	49.49	5	0.24	2073	100.00
Not Specified	86	60.56	39	27.46	17	11.97	142	100.00	8	38.10	11	52.38	2	9.52	21	100.00
Total	3041	70.84	1205	28.07	47	1.09	**4293**	**100.00**	2440	49.61	2461	50.04	17	0.35	**4918**	**100.00**
Spikevax (Moderna)																
2 Months-2 Years	0	0.00	0	0.00	0	0.00	0	0.00	8	0.00	4	0.00	0	0.00	12	100.00
3-11 Years	0	0.00	0	0.00	0	0.00	0	0.00	343	0.00	287	0.00	5	0.79	635	100.00
12-17 Years	69	92.00	6	8.00	0	0.00	75	100.00	39	0.00	45	0.00	0	0.00	84	100.00
18-64 Years	913	79.39	231	20.09	6	0.52	1150	100.00	0	0.00	2	100.00	0	0.00	2	100.00
65-85 Years	27	48.21	29	51.79	0	0.00	56	100.00	4	50.00	4	50.00	0	0.00	8	100.00
85+ Years	1	33.33	2	66.67	0	0.00	3	100.00	394	53.17	342	46.15	5	0.67	741	100.00

Not Specified	11	55.00	7	35.00	2	10.00	20	100.00	0	0.00	0	0.00	0	0.00	0	-
Total	1021	78.30	275	21.09	8	0.61	**1304**	**100.00**	788	53.17	684	46.15	10	0.67	**1482**	**100.00**
Overall (both mRNA vaccines)																
2 Months-2 Years	0	0.00	0	0.00	0	0.00	0	-	75	64.10	42	35.90	0	0.00	117	100.00
3-11 Years	4	66.67	2	33.33	0	0.00	6	100.00	1141	49.91	1135	49.65	10	0.44	2286	100.00
12-17 Years	576	87.41	78	11.84	5	0.76	659	100.00	203	54.42	170	45.58	0	0.00	373	100.00
18-64 Years	3215	72.56	1187	26.79	29	0.65	4431	100.00	307	46.17	353	53.08	5	0.75	665	100.00
65-85 Years	157	50.16	154	49.20	2	0.64	313	100.00	58	46.77	66	53.23	0	0.00	124	100.00
85+ Years	13	50.00	13	50.00	0	0.00	26	100.00	1436	51.03	1368	48.61	10	0.36	2814	100.00
Not Specified	97	59.88	46	28.40	19	11.73	162	100.00	8	38.10	11	52.38	2	9.52	21	100.00
Total	4058	72.55	1480	26.46	55	0.98	**5593**	**100.00**	3228	50.44	3145	49.14	27	0.42	**6400**	**100.00**

Table 4: Results of studies identified by systematic review, including the number of events, fatal cases, sex, and vaccine dose.

	Myocarditis		Myopericarditis		Pericarditis		Total cases		Fatal cases		Males (where specified)		Females (where specified)		Single dose		Two doses		Dose unspecified	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
1	21	43.75	27	56.25	0	0.00	48	100.00	NR		NR		NR		NR		NR		NR	
2	1241	54.94	851	37.67	167	7.39	2259	100.00	22	45.83	1555	68.84	722	31.96	NR		NR		NR	
3	33	100.00	0	0.00	0	0.00	33	100.00	NR		29	87.88	4	12.12	6	18.18	27	81.82	0	0
4	20	36.36	0	0.00	35	63.64	55	100.00	NR		42	76.36	15	27.27	NR		NR		NR	
5	0	0.00	4	100.00	0	0.00	4	100.00	NR		2	50	2	50	3	75	1	25	0	0
6	0	0.00	10	100.00	0	0.00	10	100.00	NR		6	60	6	60	3	30	7	70	0	0
7	191	78.93	2	0.83	49	20.25	242	100.00	1	0.41	205	84.71	37	15.29	37	15.29	68	28.1	139	57.44
8	21	100.00	0	0.00	0	0.00	21	100.00	NR		17	80.95	4	19.05	NR		NR		NR	
9	1226	100.00	0	0.00	0	0.00	1226	100.00	0	0.00	923	75.29	289	23.57	263	21.45	831	67.78	0	0
10	0	0.00	12	100.00	0	0.00	12	100.00	0	0.00	NR		NR		NR		NR		NR	
11	1579	59.77	0	0.00	1063	40.23	2642	100.00	NR		1906	72.14	736	27.86	NR		NR		NR	
12	397	100.00	0	0.00	0	0.00	397	100.00	0	0.00	NR		NR		NR		NR		NR	
13	48	69.57	21	30.43	0	0.00	69	100.00	NR		NR		NR		NR		NR		NR	
14	63	100.00	0	0.00	0	0.00	63	100.00	NR		58	92.06	5	7.94	1	1.59	62	98.41	0	0
15	156	100.00	0	0.00	0	0.00	156	100.00	5	3.21	131	83.97	74	47.44	NR		NR		NR	
16	0	0.00	34	100.00	0	0.00	34	100.00	NR		29	85.29	5	14.71	9	26.47	24	70.59	1	2.94
17	0	0.00	20	100.00	0	0.00	20	100.00	1	5.00	15	75	6	30	13	65	7	35	0	0
18	20	100.00	0	0.00	0	0.00	20	100.00	NR		12	60	8	40	5	25	15	75	0	0
19	0	0.00	20	100.00	0	0.00	20	100.00	NR		NR		NR		NR		NR		NR	
20	0	0.00	2038	100.00	0	0.00	2038	100.00	NR		1474	72.33	535	26.25	NR		NR		NR	
21	43	100.00	0	0.00	0	0.00	43	100.00	NR		38	88.37	5	11.63	7	16.28	36	83.72	0	0
22	182	100.00	0	0.00	0	0.00	182	100.00	1	0.55	NR		NR		0	0	142	78.02	40	21.98
23	0	0.00	12	80.00	3	20.00	15	100.00	0	0.00	13	86.67	2	13.33	8	53.33	7	46.67	0	0

24	4	100.00	0	0.00	0	0.00	4	100.00	0	0.00	4	100	0	0	2	50	2	50	0	0
25	1625	70.38	0	0.00	684	29.62	2309	100.00	0	0.00	1334	57.77	290	12.56	273	11.82	1265	54.79	0	0
26	158	54.11	0	0.00	134	45.89	292	100.00	NR		173	59.25	119	40.75	153	52.4	139	47.6	0	0
27	0	0.00	1072	100.00	0	0.00	1072	100.00	NR		NR		NR		NR		NR		NR	
28	15	100.00	0	0.00	0	0.00	15	100.00	NR		15	100	0	0	2	13.33	13	86.67	0	0
29	146	100.00	0	0.00	0	0.00	146	100.00	NR		126	86.3	20	13.7	12	8.22	134	91.78	0	0
30	38	100.00	0	0.00	0	0.00	38	100.00	NR		NR		NR		8	21.05	30	78.95	0	0
31	54	100.00	0	0.00	0	0.00	54	100.00	NR		51	94.44	3	5.56	17	31.48	37	68.52	0	0
32	14	41.18	11	32.35	9	26.47	34	100.00	0	0.00	28	82.35	6	17.65	15	44.12	19	55.88	0	0
Total	7295		4134		2144		13573		30		8186		2893		837		2866		180	
Average (%)		59.66		32.42		7.92		100.00		4.58		78.33		22.86		29.00		64.72		4.12

Table 5a: Myocarditis and pericarditis events reported to VAERS following Pfizer/BioNTech COVID-19 vaccine (Comirnaty), by dose. Datalock point 14 March 2022. Percentages per age group are presented.

Age Group	Myocarditis								Pericarditis							
	Male		Female		Sex Not Specified		Total		Male		Female		Sex Not Specified		Total	
	n	%	n	%	n	%	N	%	n	%	n	%	n	%	N	%
Dose 1																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	1	0.53	0	0.00	0	0.00	1	0.30
6-17 Years	95	37.55	13	10.24	0	0.00	108	28.20	28	14.81	10	7.09	0	0.00	38	11.48
18-29 Years	69	27.27	23	18.11	0	0.00	92	24.02	56	29.63	21	14.89	0	0.00	77	23.26
30-39 years	37	14.62	28	22.05	1	33.33	66	17.23	38	20.11	26	18.44	0	0.00	64	19.34
40-49 years	15	5.93	18	14.17	0	0.00	33	8.62	12	6.35	23	16.31	0	0.00	35	10.57
50-59 years	8	3.16	19	14.96	0	0.00	27	7.05	21	11.11	27	19.15	0	0.00	48	14.50
60-64 years	3	1.19	8	6.30	0	0.00	11	2.87	6	3.17	15	10.64	0	0.00	21	6.34
65-79 Years	14	5.53	10	7.87	0	0.00	24	6.27	22	11.64	13	9.22	0	0.00	35	10.57
80+ Years	0	0.00	3	2.36	0	0.00	3	0.78	3	1.59	2	1.42	0	0.00	5	1.51
Not Specified	12	4.74	5	3.94	2	66.67	19	4.96	2	1.06	4	2.84	1	100.00	7	2.11
Total	253	100.00	127	100.00	3	100.00	**383**	**100.00**	189	100.00	141	100.00	1	100.00	**331**	**100.00**
Dose 2																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.59	0	0.00	1	0.19
3-5 Years	2	0.27	0	0.00	0	0.00	2	0.21	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	305	40.99	37	18.05	1	14.29	343	35.88	83	23.12	11	6.51	0	0.00	94	17.67
18-29 Years	210	28.23	47	22.93	1	14.29	258	26.99	105	29.25	15	8.88	0	0.00	120	22.56
30-39 years	84	11.29	34	16.59	0	0.00	118	12.34	62	17.27	32	18.93	0	0.00	94	17.67
40-49 years	41	5.51	29	14.15	0	0.00	70	7.32	27	7.52	30	17.75	0	0.00	57	10.71
50-59 years	17	2.28	26	12.68	0	0.00	43	4.50	32	8.91	31	18.34	0	0.00	63	11.84

60-64 years	6	0.81	6	2.93	0	0.00	12	1.26	7	1.95	17	10.06	0	0.00	24	4.51
65-79 Years	21	2.82	14	6.83	0	0.00	35	3.66	28	7.80	19	11.24	1	25.00	48	9.02
80+ Years	3	0.40	0	0.00	0	0.00	3	0.31	6	1.67	3	1.78	0	0.00	9	1.69
Not Specified	55	7.39	12	5.85	5	71.43	72	7.53	9	2.51	10	5.92	3	75.00	22	4.14
Total	744	100.00	205	100.00	7	100.00	**956**	**100.00**	359	100.00	169	100.00	4	100.00	**532**	**100.00**
Dose 3																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	34	32.08	4	12.12	0	0.00	38	26.57	10	18.87	0	0.00	0	0.00	10	9.01
18-29 Years	29	27.36	9	27.27	0	0.00	38	26.57	10	18.87	5	8.93	0	0.00	15	13.51
30-39 years	13	12.26	4	12.12	0	0.00	17	11.89	5	9.43	13	23.21	0	0.00	18	16.22
40-49 years	2	1.89	5	15.15	0	0.00	7	4.90	7	13.21	17	30.36	0	0.00	24	21.62
50-59 years	7	6.60	4	12.12	0	0.00	11	7.69	4	7.55	7	12.50	0	0.00	11	9.91
60-64 years	2	1.89	3	9.09	0	0.00	5	3.50	1	1.89	6	10.71	0	0.00	7	6.31
65-79 Years	12	11.32	3	9.09	2	50.00	17	11.89	11	20.75	5	8.93	1	50.00	17	15.32
80+ Years	2	1.89	0	0.00	0	0.00	2	1.40	3	5.66	1	1.79	0	0.00	4	3.60
Not Specified	5	4.72	1	3.03	2	50.00	8	5.59	2	3.77	2	3.57	1	50.00	5	4.50
Total	106	100.00	33	100.00	4	100.00	**143**	**100.00**	53	100.00	56	100.00	2	100.00	**111**	**100.00**
Dose 4+																
60-64 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	100.00	0	0.00	2	100.00
Total	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	100.00	0	0.00	2	100.00
Unknown dose																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	91	36.40	13	18.84	1	4.35	105	30.70	24	20.17	2	3.13	1	25.00	27	14.44
18-29 Years	96	38.40	23	33.33	0	0.00	119	34.80	46	38.66	10	15.63	0	0.00	56	29.95

30-39 years	23	9.20	3	4.35	1	4.35	27	7.89	11	9.24	7	10.94	0	0.00	18	9.63
40-49 years	10	4.00	7	10.14	0	0.00	17	4.97	10	8.40	13	20.31	0	0.00	23	12.30
50-59 years	9	3.60	7	10.14	0	0.00	16	4.68	7	5.88	8	12.50	0	0.00	15	8.02
60-64 years	2	0.80	4	5.80	2	8.70	8	2.34	6	5.04	3	4.69	0	0.00	9	4.81
65-79 Years	5	2.00	4	5.80	0	0.00	9	2.63	6	5.04	13	20.31	1	25.00	20	10.70
80+ Years	0	0.00	1	1.45	0	0.00	1	0.29	0	0.00	3	4.69	0	0.00	3	1.60
Not Specified	14	5.60	7	10.14	19	82.61	40	11.70	9	7.56	5	7.81	2	50.00	16	8.56
Total	250	100.00	69	100.00	23	100.00	342	100.00	119	100.00	64	100.00	4	100.00	187	100.00
Grand Total	1353		434		37		**1824**		720		432		11		**1162**	

Table 5b: Myocarditis and pericarditis events reported to VAERS following Moderna COVID-19 vaccine (Spikevax), by dose. Datalock point 14 March 2022. Percentages per age group are presented.

Age Group	Myocarditis								Pericarditis							
	Male		Female		Sex Not Specified		Total		Male		Female		Sex Not Specified		Total	
	n	%	n	%	n	%	N	%	n	%	n	%	n	%	N	%
Dose 1																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	1	0.56	0	0.00	0	0.00	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00
18-29 Years	74	41.11	18	18.00	0	0.00	92	32.17	33	32.35	23	20.00	0	0.00	56	25.23
30-39 years	42	23.33	18	18.00	0	0.00	60	20.98	15	14.71	17	14.78	0	0.00	32	14.41
40-49 years	16	8.89	21	21.00	0	0.00	37	12.94	21	20.59	20	17.39	0	0.00	41	18.47
50-59 years	15	8.33	16	16.00	1	16.67	32	11.19	12	11.76	19	16.52	0	0.00	31	13.96
60-64 years	3	1.67	15	15.00	0	0.00	18	6.29	7	6.86	12	10.43	0	0.00	19	8.56
65-79 Years	10	5.56	11	11.00	0	0.00	21	7.34	11	10.78	16	13.91	2	40.00	29	13.06
80+ Years	2	1.11	1	1.00	0	0.00	3	1.05	0	0.00	5	4.35	0	0.00	5	2.25
Not Specified	17	9.44	0	0.00	5	83.33	22	7.69	3	2.94	3	2.61	3	60.00	9	4.05
Total	180	100.00	100	100.00	6	100.00	286	100.00	102	100.00	115	100.00	5	100.00	222	100.00
Dose 2																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	2	0.72	0	0.00	0	0.00	2	0.52	1	0.55	0	0.00	0	0.00	1	0.33
18-29 Years	152	54.48	29	29.00	1	20.00	182	47.40	63	34.81	24	19.67	0	0.00	87	28.52
30-39 years	57	20.43	15	15.00	0	0.00	72	18.75	30	16.57	11	9.02	0	0.00	41	13.44
40-49 years	24	8.60	24	24.00	0	0.00	48	12.50	20	11.05	21	17.21	0	0.00	41	13.44
50-59 years	20	7.17	13	13.00	0	0.00	33	8.59	25	13.81	24	19.67	0	0.00	49	16.07
60-64 years	6	2.15	5	5.00	0	0.00	11	2.86	10	5.52	12	9.84	0	0.00	22	7.21

65-79 Years	13	4.66	12	12.00	0	0.00	25	6.51	26	14.36	26	21.31	0	0.00	52	17.05
80+ Years	1	0.36	1	1.00	0	0.00	2	0.52	4	2.21	4	3.28	0	0.00	8	2.62
Not Specified	4	1.43	1	1.00	4	80.00	9	2.34	2	1.10	0	0.00	2	100.00	4	1.31
Total	279	100.00	100	100.00	5	100.00	**384**	**100.00**	181	100.00	122	100.00	2	100.00	**305**	**100.00**
Dose 3																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	1	1.96	0	0.00	0	0.00	1	1.16	0	0.00	0	0.00	0	0.00	0	0.00
18-29 Years	29	56.86	8	22.86	0	0.00	37	43.02	10	29.41	6	16.22	0	0.00	16	22.54
30-39 years	9	17.65	10	28.57	0	0.00	19	22.09	4	11.76	7	18.92	0	0.00	11	15.49
40-49 years	6	11.76	4	11.43	0	0.00	10	11.63	5	14.71	8	21.62	0	0.00	13	18.31
50-59 years	2	3.92	4	11.43	0	0.00	6	6.98	7	20.59	5	13.51	0	0.00	12	16.90
60-64 years	1	1.96	2	5.71	0	0.00	3	3.49	1	2.94	3	8.11	0	0.00	4	5.63
65-79 Years	3	5.88	6	17.14	0	0.00	9	10.47	6	17.65	6	16.22	0	0.00	12	16.90
80+ Years	0	0.00	1	2.86	0	0.00	1	1.16	1	2.94	2	5.41	0	0.00	3	4.23
Not Specified	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total	51	100.00	35	100.00	0	0.00	86	100.00	34	100.00	37	100.00	0	0.00	71	100.00
Dose 4+																
40-49 Years	0	0.00	1	100.00	0	0.00	1	100.00	0	0.00	0	0.00	0	0.00	0	0.00
Total	0	0.00	1	100.00	0	0.00	1	100.00	0	0.00	0	0.00	0	0.00	0	0.00
Unknown dose																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	1	0.74	1	3.03	2	25.00	4	2.27	0	0.00	0	0.00	0	0.00	0	0.00
18-29 Years	62	45.93	9	27.27	0	0.00	71	40.34	24	32.88	9	30.00	0	0.00	33	30.28
30-39 years	27	20.00	8	24.24	0	0.00	35	19.89	10	13.70	3	10.00	1	16.67	14	12.84
40-49 years	16	11.85	1	3.03	0	0.00	17	9.66	11	15.07	5	16.67	0	0.00	16	14.68

50-59 years	4	2.96	4	12.12	0	0.00	8	4.55	8	10.96	4	13.33	0	0.00	12	11.01
60-64 years	5	3.70	2	6.06	0	0.00	7	3.98	6	8.22	4	13.33	1	16.67	11	10.09
65-79 Years	3	2.22	6	18.18	0	0.00	9	5.11	11	15.07	5	16.67	0	0.00	16	14.68
80+ Years	2	1.48	1	3.03	0	0.00	3	1.70	1	1.37	0	0.00	0	0.00	1	0.92
Not Specified	15	11.11	1	3.03	6	75.00	22	12.50	2	2.74	0	0.00	4	66.67	6	5.50
Total	135	100.00	33	100.00	8	100.00	176	100.00	73	100.00	30	100.00	6	100.00	109	100.00
Grand Total	645		269		19		**933**		390		304		13		**707**	

Table 6: Details of each study identified by systematic review which met the inclusion criteria.

	First author & citation	Study design	Study period	Vaccine	Population	No. cases in exposed to mRNA vaccine	Diagnostic criteria	Percentage of cases who were male	Age of cases	Vaccine dose	RR (95% CI)	Incidence (95% CI)
1	Barda (48)	Cohort with unvaccinated comparator	December 2020 - May 2021	Comirnaty	Israel, electronic health records	Myocarditis n=21; Pericarditis n=27		NR	NR	NR	Myocarditis = 3.24 (1.55 to 12.44); Pericarditis = 1.27 (0.68 to 2.31)	NC
2	Chouchana (25)	Analysis of VigiBase spontaneous reports	Vaccine launch - end June 2021	mRNA COVID vaccine	Vigibase reports	Myocarditis n=1241; Pericarditis n=851; Myo-pericarditis n=167; Pleuro-pericarditis n=18		68.30%	Median 33 (21–54) years	NR	NC	NC
3	Chua (49)	Population cohort study	14 June 2021 - 4 September 2021	Comirnaty	Hong Kong adolescents, electronic health records	n=33 cases (myocarditis/ pericarditis)		87.88%	Median 15.25 years	81.82% followed 2nd dose	NC	Overall = 18.52 (95% CI 11.67–29.01); Males = 32.29 (95% CI 22.78–45.4); Females = 4.53 (95% CI 1.76–11.11)
4	Das (50)	Cross sectional study of 25 children aged 12-18 years diagnosed with probable myopericarditis following COVID-19 mRNA vaccination	10 May 2021 - 20 June 2021	Comirnaty	Adolescents presenting at 8 US centres	n=25 (myo-pericarditis)		88%	Range 12-17 years	88% followed 2nd dose	NC	NC

5	Diaz (51)	Retrospective cohort	Vaccine launch - 25 May 2021	mrNA COVID vaccine plus AZ vaccine	40 US hospitals, electronic health records	Myocarditis n=20; pericarditis n=35	Myocarditis75%; pericarditis 73%	Myocarditis cases median 36 (26.3-48.3) years; Pericarditis cases median 59 (46-69) years	NR	NC	NC
6	Eggebrecht (52)	Cohort	27 December 2020 - 3 September 2021	All COVID vaccines	113 patients at cardiology unit	Comirnaty cases n=85; Spikevax n=13	56%	Average age 45.9 years, 95% CI 43.2–48.7	57% followed 2nd dose	NC	NC
7	Farahmand (26)	Cohort	3 August 2020 – 21 May 2021	All COVID vaccines	Patients and employees of the Beth Israel Deaconess Medical Center (BIDMC), electronic health records	n=7	50.00%	Participants aged 25 years and older	NR	Age adjusted rate ratio = 9.7 (p=0.04)	NC
8	Foltran (53)	Analysis of VigiBase spontaneous reports	1 January - 14 September 2021	mRNA COVID vaccines	Vigibase reports for adolescents aged 12-17 years	n=242 cases (pericarditis and/or myocarditis)	85%	Mean 15.8 (+/- 1.4yrs)	1 or 2 doses	NC	NC
9	Fronza (54)	Retrospective cohort	December 2019 – November 2021	All COVID vaccines	Consecutive adults referred to a tertiary hospital network for MRI	Spikevax n=12; Comirnaty n=9	81%	Mean (SD) 31 (14) years	17 followed 2nd dose	NC	NC
10	Gargano (55)	Analysis of VAERS spontaneous reports	29 December 2020 – 11 June 2021	mRNA COVID vaccines	VAERS reports	n=1226	76.2% of 1212 cases where sex available	Median age 26 years (range 12–94 years)	76% followed 2nd dose (where dose was reported)	NC	NC
11	Golino (56)	Observational study	June - August 2021	mRNA COVID vaccines	Hospital admissions, University of Insubria, Varese, Italy	n=12 (myo-pericarditis)	33% of cases were young males	Males aged 29 (+/- 12) years	NR	NC	NC
12	Hajjo (39)	VAERS analysis	Vaccine launch – 2 September 2021	All COVID vaccines	VAERS reports	Myocarditis = 1579; Pericarditis = 1063	myo = 77%, peri = 65%	Range 6-80+ years	1-3 doses	NC	NC

13	Hause (12)	VAERS & V-Safe analysis	14 December 2020 – 16 July 2021	Comirnaty	VAERS and V-Safe reports for adolescents	n=379 (myocarditis)	NR	NR	NR	NC	NC
14	Husby (57)	Population-based cohort study	1 October 2020 – 5 October 2021	All COVID vaccines	Danish health records databases (all individuals in Denmark aged 12 and over)	Comirnaty n=48; Spikevax n=21	NR	NR	NR	NC	Absolute rate within 28 days of vaccination: Overall = 1.7 (95% CI 1.3 to 2.2) per 100,000 vaccinated individuals. Comirnaty = 1.4 (1.0 to 1.8) per 100,000 Spikevax = 4.2 (2.6 to 6.4) per 100,000
15	Jain (27)	Retrospective multicentre study	March 2021 – June 2021	mRNA COVID vaccines	Patients <21 years presenting to 16 US hospitals	Comirnaty n=59; Spikevax n=4	92%	Mean 15.6 ± 1.8 years (range 12 – 20 years)	62 cases followed 2nd dose	NC	NC
16	Kerneis (58)	Vigibase analysis	1967 – 7 May 2021	All COVID vaccines	Vigibase reports	Comirnaty n=151; Spikevax n=51	63.90%	Median 35 (IQR 25-50) years	NR	NC	NC
17	Klein (28)	Vaccine Safety Datalink analysis	14 December 2020 – 26 June 2021	mRNA COVID vaccines	Electronic health records	n=87 (myocarditis/ pericarditis)	85%	Range 12-39 years	NR	NC	NC
18	Knowlton (59)	Cohort / Case-crossover	15 December 2020 – 15 June 2021	All COVID vaccines	Adult patients presenting at Intermountain Healthcare	Comirnaty n=5; Spikevax n=15	71.40%	Median (IQR) 56 (28-70) years	NR	Within 60 days RR = 1.63 (95% CI 0.95-2.71); Within 30 days RR=2.05 (95% CI 1.17-3.48)	NC
19	Kravchenko (60)	Retrospective cohort	NR	mRNA COVID-19 vaccines	All patients referred for cardiac MRI to the Department of Diagnostic and Interventional Radiology,	Comirnaty n=19; Spikevax n=1	60%	Mean age 28 ± 12 years	75% followed 2nd dose	NC	NC

					University Hospital Bonn						
20	Lai (61)	Case-control	23 February – 2 August 2021	Comirnaty and Sinovac CoronaVac	Patients aged 12 and over, electronic health records provided by the Hospital Authority (HA) of Hong Kong; linked with population-based vaccination records	Comirnaty n=20	62.5% of 160 carditis cases overall	Mean (SD) age 57.48 (24.23) years overall for vaccinated and unvaccinated participants	13.1% followed 2nd dose	Carditis aOR= 3.57 (95% CI 1.93 - 6.60)	NC
21	Li (49)	VAERS analysis	11 December 2020 – 13 August 2021	All COVID vaccines	VAERS reports	Comirnaty n=1335 cases; Spikevax n=703	Spikevax = 69.6%, Comirnaty = 73.8%	Spikevax recipients aged 18 and older, Comirnaty recipients aged 12 and older	63.47% followed 2nd dose	NC	Incidence rate = 5.98 (95% CI = 5.73–6.24) cases per million doses administered
22	Li (29)	Cohort	10 March – 18 October 2021	Comirnaty	Hong Kong adolescents, electronic health records	n=43 (myocarditis)	88%	Mean (SD) 14.86 (1.46) years	84% followed 2nd dose	NC	NC
23	Mevorach (62)	Retrospective cohort	20 December 2020 – 31 May 2021	Comirnaty	Medical records, Ministry of Health database (Israel)	n=142 (myocarditis)	91% of the 95 cases for whom age and sex were available	16 years and older	91% followed 2nd dose	Rate Ratio=2.35 (95% CI, 1.10 to 5.02)	NC
24	Nygaard (63)	Prospective nationwide population-based cohort study	15 May 2021 – 15 September 2021	mRNA COVID vaccines	Hospitalised adolescents	Comirnaty n=15	87%	Range 13-17 years	47% after 2nd dose	NC	Males: 97 per million Females: 16 per million
25	Oh (64)	Retrospective observational study	1 June 2021 – 15 October 2021	mRNA COVID vaccines	Patients presenting at the Incheon and Daejeon hospitals' emergency departments	n=4 (myocarditis)	100%	Range 17-49 years	50% after 2nd dose	NC	NC
26	Oster (65)	VAERS analysis	December 2020 – August 2021	mRNA COVID vaccines	VAERS reports	n=1626 (myocarditis)	82%	Median = 21 years (IQR 16-31)	82% after 2nd dose	NC	NC

27	Patone (66)	Population-based cohort study	NR	Comirnaty or AZ	England	Myocarditis n=397; Pericarditis n=356	Myocarditis = 50% following 1st dose, 57.8% following 2nd dose; Pericarditis = 62.7% following 1st dose, 69.3% following 2nd dose	Myocarditis 1st dose mean (SD) 55.2 (22.0) years, myocarditis 2nd dose mean (SD) 61 (22.8) years; Pericarditis 1st dose mean (SD) 57.6 (20.1) years, Pericarditis 2nd dose mean (SD) 63.2 (18.7) years	52.1% received 1st dose only	Myocarditis 1st dose IRR=1.31 (95% CI 1.03 - 1.66); Myocarditis 2nd dose IRR=1.30 (95% CI 0.98 - 1.72); Pericarditis - No association	NC
28	Sa (67)	observational study (VAERS)	14th Dec 2020 – 30th Sept 2021	Comirnaty Spikevax or Janssen	US population, aged over 18yrs	Comirnaty n=1072; Spikevax n=791	NR	n=1573 18-64 years, n=193 65 years and older	NR	NC	NC
29	Simone (68)	retrospective population-based cohort study	14 December 2020 – 20 July 2021	mRNA COVID vaccines	Kaiser Permanente Southern California (KPSC) members aged 18 years and older	n=15 (myocarditis)	100%	Median (IQR) 52 (32-59) years	86.7% followed 2nd dose	1st dose: RR=0.38 (95%CI 0.05-1.40) 2nd dose: RR=2.7 (95% CI 1.4-4.8)	NC
30	Truong (69)	Retrospective cohort	Until 4 July 2021	All COVID vaccines	adolescents and young adults <21 years old, presenting at 26 paediatric medical centres across US and Canada	Comirnaty n=131, Spikevax n=5	90.60%	Median 15.8 (range 12.1-20.3) years	91.4% followed 2nd dose	NC	NC
31	Tsun Lai (70)	population-based retrospective cohort study	1 January 2018 – 30 September 2021	Comirnaty or CoronaVac	Inpatients 12 years and older (Hong Kong)	N=38 (myocarditis)	NR	NR	1 or 2 doses	1st dose: IRR=9.15 (95% CI 1.14-73.16); 2nd dose: IRR=29.61 (95% CI 4.04-217.07)	
32	Witberg (71)	Population-based cohort study	42 days after dose 1	Comirnaty	Clalit Health Services, electronic health	n=54 (myocarditis)	94%	Median (IQR) = 27 (21-35) years	1 dose	NC	Overall: 2.13 (95% CI 1.56-

					records for patients aged 16 years or older						2.70) per 100,000
33	Yap (72)	Reports to Singapore's vaccine safety committee	January 2021 – July 2021	mRNA COVID vaccines	Singapore	n=34 (pericarditis, myocarditis, or concomitant pericarditis and myocarditis)	82.40%	Myocarditis median 23 (range 12-55) years	64% followed 2nd dose	NC	NC

NR = Not Reported; NC = Not calculated; SD = Standard Deviation; CI = Confidence Interval; aOR = Adjusted Odds Ratio

Declarations

Transparency statement

The manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, and that no important aspects of the study have been omitted.

Ethics approval

Ethics approval was not required.

Funding

No external funding was received for the preparation of this manuscript.

Conflicts of interest

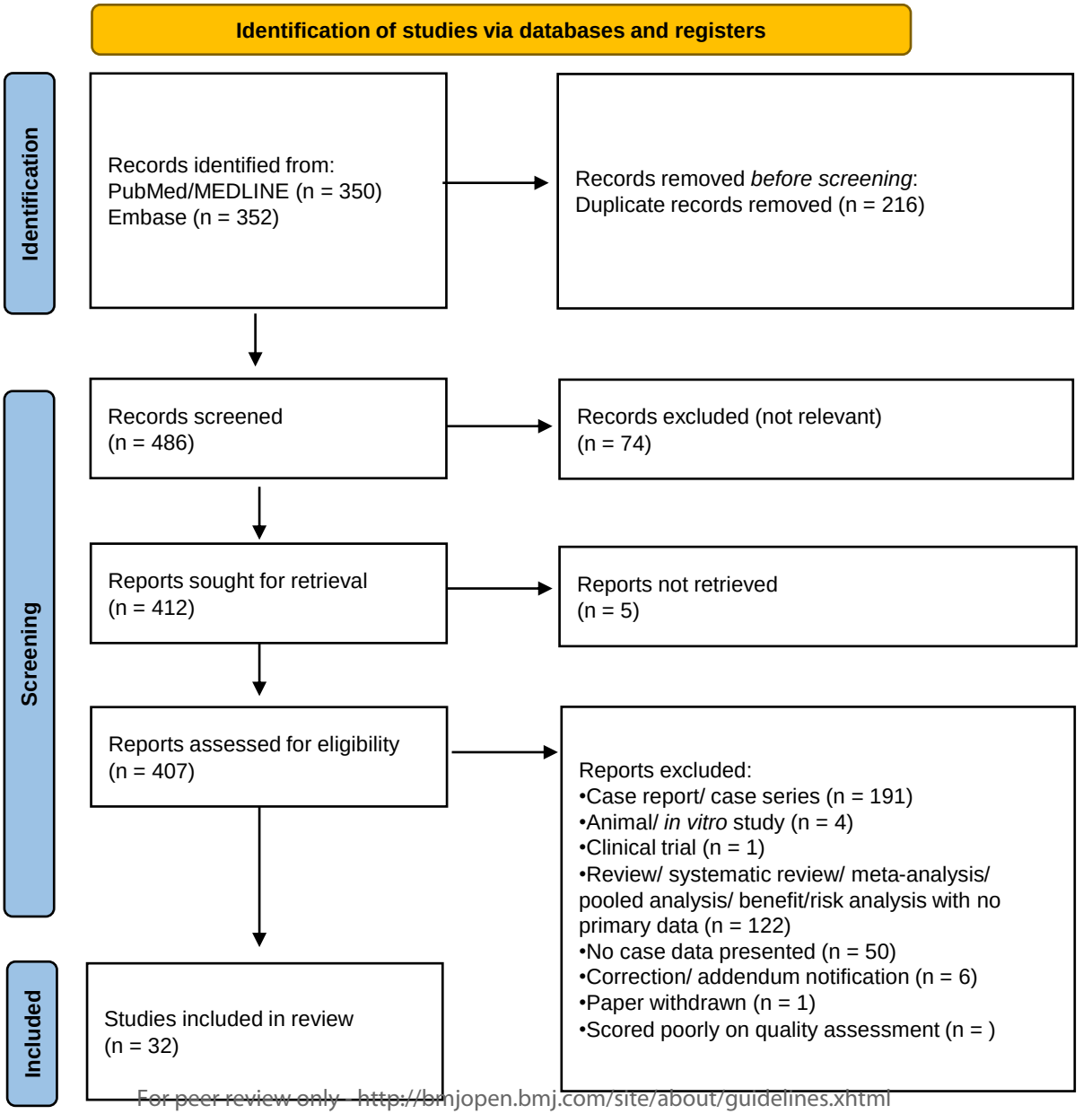
All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: The Drug Safety Research Unit (DSRU) is a registered independent charity (No. 327206) associated with the University of Portsmouth. The DSRU receives donations and grants from pharmaceutical companies; however, the companies have no control over the conduct or publication of its studies. The DSRU has received grants to conduct unconditional studies on the Oxford/AstraZeneca COVID-19 vaccine and is in negotiations to receiving grants for conducting CPRD studies for Pfizer, Moderna, and Janssen COVID-19 vaccines. The DSRU has conducted benefit-risk studies on products for COVID-19, including remdesivir, lopinavir/ritonavir, chloroquine and hydroxychloroquine, and convalescent plasma. Professor Shakir is the principal investigator for an active surveillance study for the Oxford/AstraZeneca vaccine, but this assessment is unrelated to this study. Professor Shakir has been a member of Data Safety Monitoring Boards for Ipsen, Biogen, and Diurnal. None of these companies have any involvement with COVID-19 vaccines. Professor Shakir was invited by AstraZeneca to advise on the events of thrombosis with thrombocytopenia with the COVID-19 vaccine and to be a member of an advisory committee on a safety study of the Oxford/AstraZeneca vaccine in Europe. Samantha Lane and Alison Yeomans have no conflicts of interest with regard to this study.

Authors' contributions

SL and AY were responsible for data acquisition, analyses, and interpretation. All authors were responsible for study conception, drafting and reviewing the manuscript, and approval of the final version for publication.

Data sharing

CASP checklists for assessing quality of each study included in systematic review are available on request.



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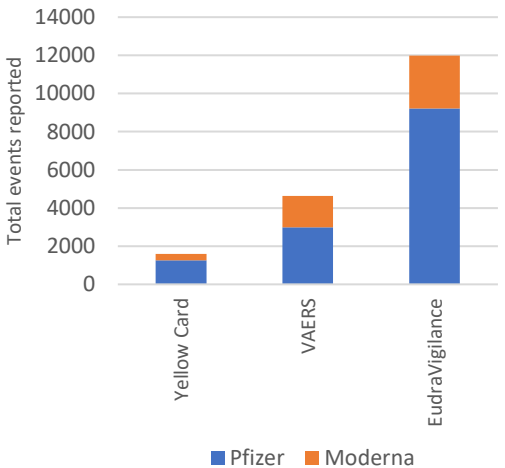

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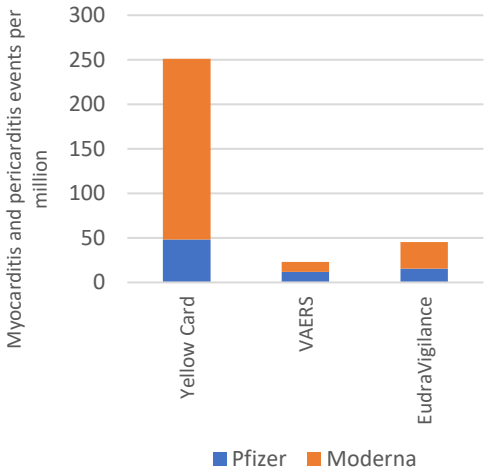

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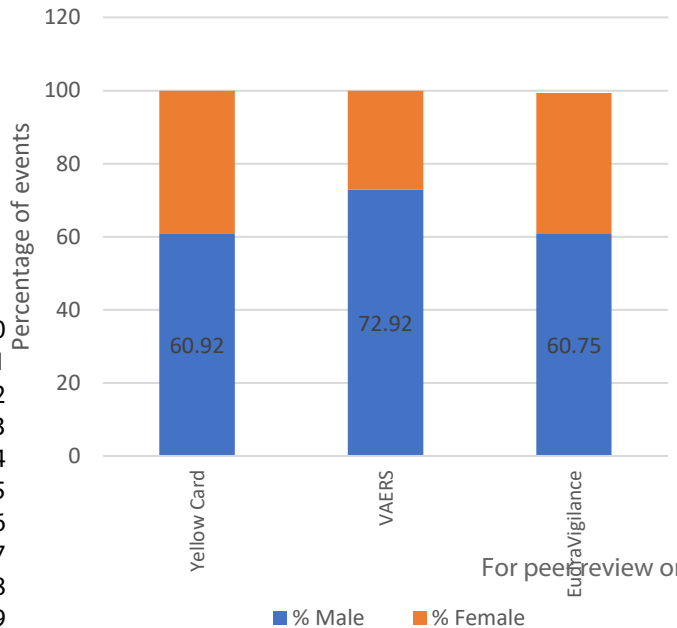

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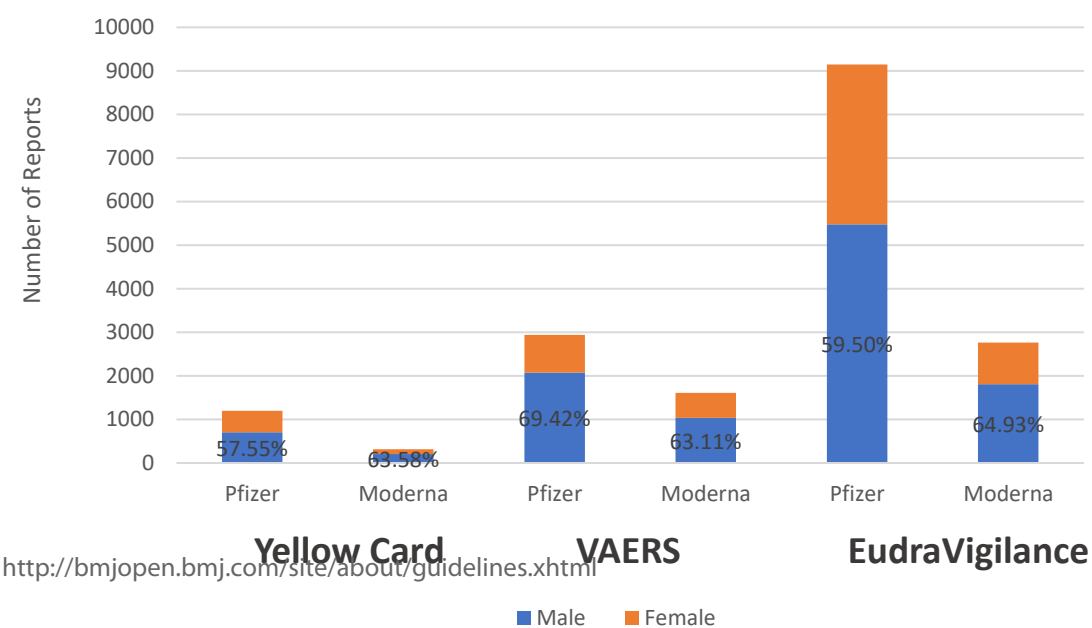

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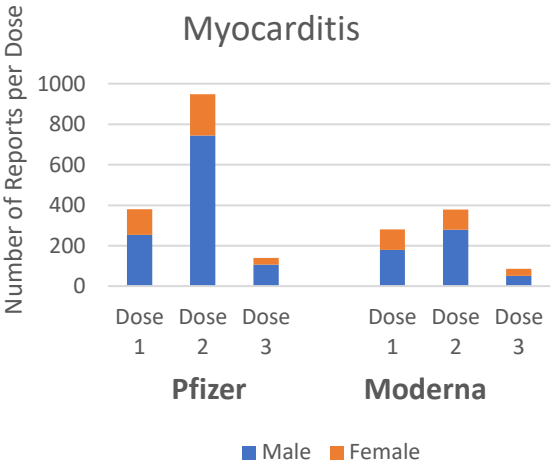

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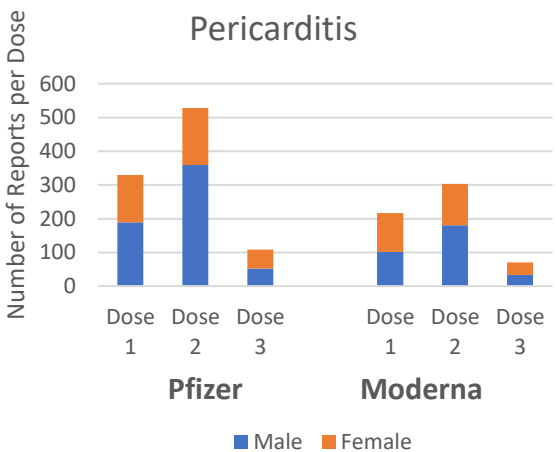

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3 & 4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	n/a – all patients spontaneously reporting events of myocarditis and pericarditis were included
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and	4 (confounders and effect modifiers not applicable)

		effect modifiers. Give diagnostic criteria, if applicable	
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	4
Bias	#9	Describe any efforts to address potential sources of bias	n/a – not possible to address bias in spontaneously reported data. Biases discussed as a limitation on page 8
Study size	#10	Explain how the study size was arrived at	n/a – all spontaneously reported events of myocarditis and pericarditis to the UK's Yellow Card scheme, US VAERS, and EEA EudraVigilance were included
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	n/a – not applicable in this study

Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	n/a – no statistical methods were applied
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	n/a – not applicable for the data used
Statistical methods	#12c	Explain how missing data were addressed	n/a – not applicable for these datasets; missing information within spontaneous reports mentioned as a limitation on page 8
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a – no analytical statistical methods applied; no sampling
Statistical methods	#12e	Describe any sensitivity analyses	n/a – no sensitivity analyses conducted
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	5 & 6; Tables 1, 2, 3a, 3b & 4

Participants	#13b	Give reasons for non-participation at each stage	n/a – all patients reporting myocarditis and pericarditis to spontaneous reporting systems of UK, US and EEA were included up to the datalock point
Participants	#13c	Consider use of a flow diagram	n/a
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	5 & 6; All tables
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	Tables 2-4
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	5 & 6; Tables 1-4
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	n/a – only descriptive statistics (counts and percentages) used

		confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	Tables 2-4
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a – not appropriate for these data as no comparator
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	5 & 6
Discussion			
Key results	#18	Summarise key results with reference to study objectives	6 & 7
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	7 & 8
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	7 - 9

Generalisability	#21	Discuss the generalisability (external validity) of the study results	9
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2 (see separate checklist for detail)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5/6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5/6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5/6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5/6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5/6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A (descriptive)
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	6-9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	Table 5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8-9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A Results presented in Table 5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9-10
	23b	Discuss any limitations of the evidence included in the review.	11
	23c	Discuss any limitations of the review processes used.	11
	23d	Discuss implications of the results for practice, policy, and future research.	11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	13
Competing interests	26	Declare any competing interests of review authors.	13

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	13-14

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

BMJ Open

Reports of myocarditis and pericarditis following mRNA COVID-19 vaccination: a systematic review of spontaneously reported data from the UK, Europe, and the US and of the scientific literature

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Cardiovascular medicine, Infectious diseases
Keywords:	COVID-19, Adverse events < THERAPEUTICS, PUBLIC HEALTH

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Reports of myocarditis and pericarditis following mRNA COVID-19 vaccination: a systematic review of spontaneously reported data from the UK, Europe, and the US and of the scientific literature

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Word count: (excluding tables): 4676

Number of tables: 7

Number of figures: 4

Abstract

Objectives: To combine spontaneously reported data from multiple countries to estimate reporting rate, and better understand risk factors for myocarditis and pericarditis following COVID-19 mRNA vaccines.

Design: Systematic review of spontaneously reported data from United Kingdom (UK), United States (US), and European Union/European Economic Area (EU/EEA) and of the scientific literature.

Data sources: UK Yellow Card scheme, Vaccine Adverse Event Reporting System (VAERS), EudraVigilance were searched from date of vaccine launch to 14-16 March 2022. PubMed/MEDLINE and Embase were searched to 15 March 2022.

Eligibility criteria: We included publicly available spontaneous reporting data for "Myocarditis" and "Pericarditis" from UK, US, and EU/EEA following COVID-19 mRNA vaccines. Pharmacoepidemiological observational studies investigating myocarditis/pericarditis following mRNA COVID-19 vaccines were included (no restrictions on language or date). Critical Appraisal Skills Programme (CASP) tools assessed study quality.

Data extraction and synthesis: Two researchers extracted data. Events of myocarditis and pericarditis were presented for each data source, stratified by vaccine, age, sex, and dose (where available). Reporting rates were calculated for myocarditis and pericarditis for each population. For published pharmacoepidemiological studies, design, participant characteristics, and study results were tabulated.

Results: Overall, 18,204 myocarditis and pericarditis events were submitted to the UK, US, and EU/EEA regulators during the study period. Males represented 62.24% (n=11,331) of myocarditis and pericarditis reports. In the UK and US, most reports concerned vaccinees aged <40 years (59.7% and 47.3% of reported events, respectively); trends in age were less clear for EU/EEA. Reports were more frequent following a second dose (47.1% of reports, where data available). Reporting rates were consistent between the data sources. Thirty-two pharmacoepidemiological studies were included; results were consistent with our spontaneous report analyses.

Conclusions: Younger vaccinees more frequently report myocarditis and pericarditis following mRNA COVID-19 vaccines than older vaccinees. Results from published literature supported the results of our analyses.

Strengths and limitations of this study

- This is the first study to bring together spontaneously reported data from the United Kingdom, United States, and Europe on myocarditis and pericarditis following mRNA COVID-19 vaccines.
- Results from this study provide evidence on the frequency of reported events of myocarditis and pericarditis following mRNA vaccines in different age groups, and by sex and vaccine dose; analyses of spontaneous reports were consolidated with results of published literature, identified by systematic review.
- Results may have been influenced by biases including different vaccination policies in each region examined, and publicity on events of myocarditis and pericarditis following mRNA vaccines.

- The study relied on outputs from spontaneous reporting systems in which the level of detail differed between the systems examined; furthermore, it is not possible to estimate incidence rates using spontaneous reports due to the lack of data on the exposed population, and there is no unvaccinated comparison group.
- There is an urgent need for further pharmacoepidemiological studies to be conducted to provide more accurate estimates of the frequency, clinical course, long term outcome, effects of treatment and impact on quality of life, to address many of the limitations of spontaneous reporting.

Introduction

Messenger RNA (mRNA) based vaccines have been extensively used world-wide in the fight against COVID19 that continues to pose a threat, with many countries initiating booster campaigns, yet these are the first in their class of vaccines to be approved for use, and as such continued monitoring of their safety is required. In the 15 months since first approval mRNA-based vaccines have had several adverse reactions documented, including myocarditis and pericarditis. Signals of myocarditis and pericarditis were first identified in Israel where there had been 148 cases of myocarditis reported within 30 days of vaccination, with the majority of these cases (n=121) reported after the second dose (1). Since the emergence of this signal, multiple countries have reported myocarditis and pericarditis following mRNA COVID-19 vaccines (2) and these events have been listed in the product information for both Pfizer-BioNTech (Comirnaty) and Moderna (Spikevax) mRNA COVID-19 vaccines (3-9). The identification of this safety signal early in the vaccination programme indicated that young males were at higher risk of developing myocarditis or pericarditis, particularly after the second dose of either mRNA based COVID-19 vaccine (2, 10-12). Myocarditis and pericarditis events following COVID-19 mRNA vaccines occur very rarely at a frequency of 10-20 events per 100,000 (13, 14), and the clinical course is typically mild with most cases making a full recovery (15).

Vaccination programmes around the world have differed in their roll-out and vaccine type used, with a general pattern that those most at risk of severe COVID-19 complications were prioritised for vaccination, followed by healthy adults and then children; in all these groups mRNA vaccines have been approved and used alongside adenovirus vector vaccines and inactivated virus vaccines around the world (4-9, 16, 17). Waves of COVID-19 infections in different countries also altered the speed of vaccine roll-out and the time interval between vaccine doses, thus interpretation of the data from several countries may reveal risk factors for myocarditis and pericarditis following exposure to COVID-19 mRNA vaccines. Here we collate spontaneous reports of myocarditis and pericarditis following COVID-19 vaccination, with a systematic review of the literature, to capture and interpret the evidence to date.

Methods

Data sources

The data sources were spontaneous reporting system outputs of the UK Yellow Card scheme, the US Vaccine Adverse Event Reporting System (VAERS) via the CDC Wonder online tool, and the EU/EEA EudraVigilance system were used to estimate the frequency of reported cases of myocarditis and pericarditis following COVID-19 Vaccine Pfizer/BioNTech (Comirnaty) and COVID-19 Vaccine Moderna (Spikevax) (18-20). These systems collect unsolicited suspected adverse events to vaccines and medications from healthcare professionals and consumers. The process of spontaneous reporting requires suspected association with the mRNA vaccine to the event by the reporting individual. For reports following a mRNA COVID-19 vaccine, all reports coded “myocarditis” and “pericarditis” which had been spontaneously reported to these systems between the date of vaccine launch and the datalock point were counted. Cases were stratified by age, sex, and vaccine dose where these data were available.

The datalock point (defined as the date that searches were ran in the database) was 14 March 2022 for VAERS and EudraVigilance, and 16 March 2022 for the Yellow Card scheme. Data from the Yellow Card scheme is released weekly, with data up to 16 March 2022 the closest release to the 14 March 2022 datalock point used for VAERS and EudraVigilance.

The number of vaccinated individuals per vaccine brand in the UK, US, and EU/EEA were obtained from the websites of the MHRA, the CDC in the US, and the European Centre for Disease Prevention and Control (ECDC) up to the date closest to the datalock point for ADR spontaneous reports (11, 21, 22). Reporting rates of myocarditis and pericarditis per million vaccines administered were calculated for those who had received at least one dose of each vaccine brand.

Literature review

A systematic literature review was conducted using PubMed/Medline and Embase literature databases. No review protocol was prepared.

The datalock point was 15 March 2022. Studies were included if they were observational in design (excluding case reports and case series), and involved at least one patient who experienced myocarditis, pericarditis, or myopericarditis following any mRNA COVID-19 vaccine (any case definition was accepted). Pre-print manuscripts were included if no peer-reviewed version was available. Studies of other designs and studies investigating other vaccines were excluded. Studies investigating cardiac effects of SARS-CoV-2 infection were excluded. No restrictions on language or date were applied.

The search terms used were:

(myocarditis OR pericarditis OR myopericarditis) AND (covid-19) AND (vaccine)

Data were extracted for study design, study period, vaccine of interest, population, number of cases of myocarditis or pericarditis, and where specified the percentage of cases who were male, age, and the vaccine dose after which the event occurred. Two reviewers extracted data. These data were tabulated.

Study quality was assessed by two reviewers, using the relevant Critical Appraisal Skills Programme (CASP) tool (23). Each checklist covers a different study design and contains a series of questions to allow systematic appraisal of the validity, results, and usefulness of results of each publication. All publications were evaluated using the appropriate CASP checklist, and all were deemed acceptable for inclusion in this systematic review.

Patient and public involvement

Patients and the public were not consulted during this study.

Results

Systematic review of the literature identified thirty-two observational studies

In order to collate information specific to address the issue identification of characteristics of myocarditis and pericarditis following COIVD-19 mRNA vaccines a detailed review of the literature was carried out, using the search terms specified in the materials of methods (Section 2.1). Initially 702 records were identified, following de-duplication, assessment for eligibility and quality 32 studies were included in our analysis (Figure 1). The information extracted in these studies has been assessed alongside the evidence from spontaneous reporting systems, below.

Myocarditis and pericarditis occur very rarely following COVID-19 mRNA vaccines

Overall, across the three spontaneous reporting databases examined covering the UK, US, and EU/EEA populations, there were a total of 18,204 events of myocarditis and pericarditis submitted to the regulators.

From the UK's MHRA Yellow Card scheme, 1260 reports were following Comirnaty administration, and 325 reports were following Spikevax (Table 1; Figure 2A). As of 16 March 2022, it was estimated that 26.2 million first doses and 23.6 million second doses of Comirnaty had been administered in the UK (11). Therefore, there were approximately 48.09 cases of myocarditis and pericarditis per million vaccinees who had received at least one dose of Comirnaty (Figure 2B). To the same date, approximately 1.6 million first doses and 1.5 million second doses of Spikevax had also been administered (11). Of those who had received at least one dose of Spikevax in the UK, 203.13 cases of myocarditis and pericarditis had been reported per million vaccinated (Figure 2B).

The US VAERS system contains 2986 reported events following Comirnaty and 1640 events following Spikevax (Table 2; Figure 2A). In the US, there had been 124.12 million vaccinees who had been fully vaccinated with Comirnaty (21) giving a reporting rate of 14.70 cases of myocarditis and 9.36 cases of pericarditis per million fully vaccinated individuals, combined to 12.03 cases of myocarditis and pericarditis per million fully vaccinated with Comirnaty (Figure 2B). There had been 75.57 million people fully vaccinated with Spikevax (21) therefore there were 12.35 cases of myocarditis reported per million fully vaccinated Spikevax recipients and 9.36 cases of pericarditis per million fully vaccinated Spikevax recipients, combined giving a reporting rate of both myocarditis and pericarditis as 10.86 per million Spikevax vaccinees (Figure 2B).

The EudraVigilance database contained the highest total reports of events with 9211 events reported following Comirnaty and 2786 following Spikevax (Table 3; Figure 2A). There had been approximately 296.05 million vaccinees who had received at least one dose of Comirnaty in the EU/EEA (22). Therefore, the reporting rates were calculated as 14.50 reports of myocarditis and 16.61 reports of pericarditis per million Comirnaty recipients, giving a combined reporting rate of 15.56 cases of myocarditis and pericarditis per million people who received at least one dose of Comirnaty (Figure 2B). For Spikevax, there had been approximately 46.56 million first doses of Spikevax administered in the EU and EEA (22). Thus, reporting rates in the EU/EEA are currently 28.01 reports of myocarditis and 31.83 reports of pericarditis per million vaccinees, giving a combined reporting rate of 29.92 per million Spikevax recipients (Figure 2B).

In total, there were 13,573 events of myocarditis and/or pericarditis reported in the observational studies identified by systematic review of the literature.

While reporting rates for myocarditis and pericarditis have differed between the spontaneous reporting databases, overall, they demonstrate that these events are very rare (defined as occurring at a rate of <1 in 10,000) (24).

Fatalities following myocarditis and pericarditis after COVID-19 mRNA vaccines

There have been cases of myocarditis and pericarditis with a fatal outcome reported to spontaneous reporting systems and in the literature. There were four fatalities in the UK (0.25% of all spontaneous reports), 62 in the US (1.3% of all reports) and 56 in the EU/EEA (0.6% of all reports). Where age of

fatal cases was reported (EudraVigilance and VAERS databases only), 85.83% (n=103) of fatal cases overall were aged 18 years or older. Five cases (4.17%) were aged under 18 years; all were myocarditis events (6.41% of all fatal myocarditis events reported). Ten percent of fatal cases had age unspecified. All fatal cases of pericarditis reported to EudraVigilance and VAERS were aged 18 years or older.

Fatal cases were reported in five of the 32 included studies identified by systematic literature review (Table 4) (25-29). Overall, 0.22% (n=30) of 13,571 myocarditis or pericarditis events reported in the literature had a fatal outcome (range 0.41-45.85%; Table 4). Characteristics of fatal cases were specified in one study (25). In this study, results indicated that fatal cases of myocarditis and pericarditis occurred in the adult population. There were 15 fatal myocarditis events (median age 60 [Interquartile Range (IQR) 56-78] years), 5 fatal pericarditis events (median age 71 [IQR 67-77] years), and two fatal myopericarditis events (aged 55 and 83 years).

Young males are more likely to suffer myocarditis and pericarditis following COVID-19 mRNA vaccination

To confirm the early evidence that young males were most susceptible to the adverse reaction of myocarditis and pericarditis (1), we compared spontaneous reporting and the literature up until 16 March 2022 to determine whether this signal has been maintained since initially identified. Of the myocarditis and pericarditis events reported to the Yellow Card scheme, 60.92% were from males with a trend towards increased frequency in younger age groups (Table 1; Figure 3A). This trend of more frequent reporting from males was similar across the three regions assessed, with 72.92% in the US and 60.75% in the EU/EEA (Figure 3A), as well as similar reporting trends between the vaccine types (Figure 3B).

Most reports of myocarditis in the US were from vaccinees aged 18-39 years (n=1303, 47.3% of 2757 reports), while in the EU 79.2% (n=4431) of reports of myocarditis where from people aged 18-64 years (Table 3). In the US, 59.39% of pericarditis events were reported from males (Table 2) and the age distribution of those who reported pericarditis was wide, covering many age categories (Table 2). In the EU, 50.43% of the reported pericarditis events occurred in males (Table 3). The trend in age was less distinct, with children (3-11 years) and the elderly (aged older than 85 years) populations accounting for 35.7% and 43.97% of reported cases, respectively (Table 3).

Analysis of the literature determined that on average 60.31% of myocarditis and/or pericarditis events following COVID-19 mRNA vaccines occurred in males (range 50.00-100.00%). Results of these studies indicate that the incidence for myocarditis and pericarditis was higher for males than for females. Due to differences in study design it was not possible to determine the age group most susceptible to myocarditis and pericarditis from the literature as some studies were focused on adults only or children only meaning appropriate comparisons could not be carried out.

Most myocarditis and pericarditis events are reported following the second mRNA vaccine dose

Analysis of data following booster programme roll out has enabled detailed analysis into the frequency of reports following each dose of a COVID-19 mRNA vaccine. Data for the US is stratified by dose and demonstrates that the majority of reported myocarditis and pericarditis events occurred following the second dose (Figures 4A, 4B). For Comirnaty, of the total 1824 myocarditis events reported to VAERS, 956 (52.41%) followed the second dose, while 383 (21.00%) were reported after a single dose of the vaccine (Table 5). Similarly, 45.78% of pericarditis events were reported to VAERS following two doses

of Comirnaty (n=532 of 1162 reported events where vaccine dose was specified; Table 5). For Spikevax, 384 of 933 (41.16%) reported events of myocarditis and 305 of the 707 (43.14%) reported events of pericarditis occurred following two doses of the vaccine (Table 6). Approximately 10% of myocarditis and pericarditis events had been reported following a third dose for both vaccines up to 14 March 2022 (Tables 5 and 6).

This data is in agreement with other studies where 64.72% (range 25.00% and 91.78%) of myocarditis and pericarditis events occurred following the second vaccine dose (Table 4).

Discussion

There have been a small number of reports of myocarditis and pericarditis following exposure to mRNA COVID-19 vaccines in each database examined, considering the number of people who have received a COVID-19 vaccine in each region. In all spontaneous reporting systems and for both mRNA vaccines, the reporting rate of myocarditis was higher than that of pericarditis. This may be true, or it may also reflect that the diagnosis of myocarditis is relatively more straightforward. In the UK and EU/EEA, reporting rates of myocarditis and pericarditis were higher following Spikevax compared with those for Comirnaty. However, this was not observed for the US. A full dose of Spikevax used for first and second doses contains 100 micrograms of mRNA nucleotides, whereas a full dose of Comirnaty contains 30 micrograms of the mRNA material (4, 5). This is one possible reason for the higher reporting rate of myocarditis and pericarditis observed for Spikevax in the UK population. A half-dose of Spikevax is used for booster vaccination doses; this still contains more genetic material than Comirnaty (4). Therefore, it will become increasingly important as more people receive third and subsequent booster doses of mRNA COVID-19 vaccines to monitor the frequency and severity of myocarditis and pericarditis following exposure to these vaccines.

The UK had the highest reporting rate for both myocarditis and pericarditis following mRNA vaccines, particularly for events following Spikevax. Reporting rates from the UK showed higher variability compared with those of the US and EU/EEA; reporting rates were higher for myocarditis and pericarditis following Spikevax in the UK, compared to EU/EEA and US reporting rates and incidence reported in the literature. This variability is potentially due to the fact that the UK MHRA Yellow Card scheme had the lowest number of spontaneous reports (Figure 1A) as well as the lowest vaccination coverage for Spikevax leading to uncertainty and variability. Analysis of multiple sources was thus essential to provide accurate reporting rates. It is possible that the UK and EU/EEA have stronger spontaneous reporting systems compared with the US, which may explain the higher reporting rates observed for this population. The frequency of events noted by regulators, the World Health Organisation, and in the vaccines' summaries of product characteristics (SmPC) suggest that myocarditis and pericarditis are very rare, occurring in less than one in 10,000 vaccine doses administered (2, 6, 7, 10, 11). Our calculated reporting rates for myocarditis and pericarditis following mRNA vaccines in each of the UK, US, and EU/EEA were consistent with this. However, underreporting of the events to regulators is possible, therefore it may be that the events of myocarditis and pericarditis are 'rare' events (more frequent than 1/10,000) rather than 'very rare' (less frequent than 1/10,000) events as suggested. Conversely greater reporting may have occurred due to the public interest in adverse reactions linked with COVID-19 vaccines, thus analysis of multiple data sources was used here to overcome these potential limitations. In October 2021, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency announced a plan to review the risk of myocarditis and pericarditis following mRNA vaccines (30). It is therefore possible that updates to the vaccines' SmPC will be required once this review is complete.

When examining the demographics of vaccinees who had reported myocarditis or pericarditis following mRNA vaccines, both events appear to more commonly affect males compared with females, particularly amongst vaccinees of younger age categories (Tables 2, 3, 5, 6). This is consistent with early reports surrounding these events, where it was suggested that younger males appear at higher risk of myocarditis and pericarditis following mRNA vaccines (1). Demographic data was available for VAERS and EudraVigilance populations separated by myocarditis and pericarditis; in these databases results were similar with more than 70% of myocarditis and more than 50% of pericarditis events reported in males (Tables 2 and 3). These results are consistent with results of pharmacoepidemiological studies in the published literature; in the studies where sex was reported, more than 60% of patients were male (Table 7) (31-36). This is an interesting finding, as it has been previously suggested that over 70% of reports to VAERS involve females (32). It is possible that the event was missed or misclassification occurred in older adults, particularly in older individuals in the three populations of interest who were vaccinated prior to the signal emerging. It is also possible that some of the symptoms of myocarditis and pericarditis, for example chest pain and breathlessness, were attributed to other cardio-respiratory conditions in older people. Nonetheless, it is known that most cases of myocarditis (any cause) occur in young adults, with males more commonly affected than females; this supports the results observed in this study (37, 38). Alternatively, vaccine roll-out in each of the regions may have affected the results observed in some of the countries, including availability of different vaccines and corresponding age distributions of those receiving each vaccine in different regions; for instance, in the UK, mRNA vaccines were more frequently used in younger age groups, while older vaccinees may have been more likely to receive an adenovirus vector vaccine.

We appreciate that there will be regional differences in COVID-19 strains as well as endemic viruses circulating in the populations, and these may have been the underlying cause of myocarditis and pericarditis in the reporting populations examined. However, it is not possible to identify or quantify these in spontaneously reported data. In order to overcome these differences, we have analysed data from three different spontaneous reporting systems and worldwide data from the literature to identify trends in this very rare event. As this is a very rare event with small numbers of people affected, it is important to bring together data from around the world to identify trends that may not be seen within one population. Further analysis is required in discrete populations, if appropriate, to better stratify patients, aiding classification of groups according to risk factors for adverse events following vaccination.

Data on vaccine dose were only available from the VAERS database. Most cases reported to VAERS followed a second dose of vaccine (Tables 5 and 6). This is consistent with the early signal which emerged in Israel, where 121 of the 148 reported cases of myocarditis occurred around the time of the second dose of COVID-19 vaccine (1). Furthermore, similar results were observed by Hajjo et al., who found only a very small number of events occurring after a third dose in their analysis of VAERS data (39).

Pharmacoepidemiological studies identified by systematic review (Table 7) were consistent with results found in spontaneously data from VAERS and EudraVigilance (Tables 2-3, 5-6). Young males more frequently reported myocarditis in each of these studies and found in our analysis of spontaneous reporting data. Furthermore, reports were more frequent following a second dose of mRNA vaccine, although time intervals between doses was not specified and may also differ between regions. Therefore, incorporation of the evidence on dosing effects from the VAERS system and the literature indicated that following the second dose was when the most myocarditis and pericarditis events occurred. Continuous monitoring of this will be required, especially following subsequent doses of mRNA vaccines.

Myocarditis has been observed historically following vaccination, including after smallpox, influenza, and hepatitis B vaccines; prior to COVID-19 0.1% of reports to VAERS between 1990 and 2018 had been in relation to myopericarditis (13). Furthermore, myocarditis is known to occur after a range of viral infections, including coronaviruses which cause Middle East Respiratory Syndrome (MERS) and COVID-19, with viral infection the most common cause of myocarditis (40-42). This study provides evidence that younger vaccinees more frequently report myocarditis and pericarditis following mRNA COVID-19 vaccines compared with older vaccinees, and reports are more frequent following the second dose. Results were consistent between each of the three data sources used. This is an important finding, because as vaccination programmes around the world progress, rates of myocarditis and pericarditis are likely to increase. The effect of booster vaccinations with mRNA COVID-19 vaccines on the development of myocarditis and pericarditis is largely unknown. Furthermore, mRNA COVID-19 vaccines (particularly Spikevax) are being supplied to the COVAX initiative for distribution throughout low- and middle-income countries, where diagnostic imaging and access to healthcare is more difficult (43, 44). Regulatory authorities should continue to monitor the effects that mRNA vaccination might have on the heart in the populations for which they are responsible. The proportions of young people are higher in low- and middle-income countries' populations compared to high income countries. Issuing diagnostic criteria and treatment protocols for myocarditis and pericarditis with mRNA COVID-19 vaccines that take into consideration the capabilities of the local healthcare system are also important.

Limitations

Vaccination policies in the three regions may have biased the results towards a higher number of adverse events reports myocarditis and pericarditis from younger vaccinees compared with older vaccinees. In each of these regions, younger people were more likely to have received mRNA vaccines, which may have contributed to higher reporting rates of myocarditis and pericarditis in younger vaccinees. The frequency of reported events per age group was presented as a crude number, and reporting rates could only be calculated as an overall estimate rather than stratified by age; based on the data available for vaccinations administered, it was not possible to determine the proportion of all vaccinees per age group who reported an event of myocarditis or pericarditis. This is very important, because it is likely that the reporting rate of myocarditis and pericarditis with mRNA COVID-19 vaccines will be higher in young people and even higher in young men if the reporting rates are stratified by age and sex. The regulatory authorities and Marketing Authorisations Holders (MAHs) need to follow up reports of these conditions with reporters to obtain as much information and make this information available publicly. Myocarditis and pericarditis following mRNA COVID-19 vaccines is an area which requires further research.

The data sources for this study were spontaneous reporting systems of the UK, US, and EEA. All spontaneous reporting systems have well-known limitations including missing information, and reporting bias caused by publicity surrounding a particular adverse event (45). Misclassification of myocarditis and pericarditis, or differing definitions of these events between the regions analysed, is also possible particularly before these events attracted publicity or among older age groups. The definition and diagnosis of "Myocarditis" and "Pericarditis" are based on the reporters' statements, and are not usually validated by the regulatory authority receiving the report. Under-reporting is a major limitation of spontaneous reporting; even with the intense publicity and global attention on COVID-19 vaccine safety, it is possible that not all cases are reported to regulatory authorities (46, 47). Furthermore, a report to spontaneous reporting systems indicates suspicion that the event was associated with the vaccine, it does not confirm that the vaccine caused the event (11, 45). Further

assessment is required to determine causality for each report. Finally, it is not possible to estimate incidence rates using spontaneous reports, and there is no unvaccinated comparison group (45).

Using publicly available data introduced some challenges, as the level of detail available was limited and varied between data sources. Data on the vaccine dose on which the reported events of myocarditis and pericarditis occurred were only available for the US VAERS population. Information contained within individual reports is not routinely made available, however these comprise important clinical information that would allow better understanding of each case. Such details should be made publicly available. Better transparency is needed to allow more robust research using spontaneous reporting to be undertaken.

Due to the limited published research into myocarditis and pericarditis following mRNA COVID-19 vaccines, we included all pharmacoepidemiological study designs (except case reports and case series) and considered all study populations and all study periods for inclusion. The purpose of systematically reviewing the literature was to determine whether results from our analyses of spontaneous reports were consistent with other evidence currently available. Due to the short time period since vaccine programmes were initiated and the heterogenous nature (regional differences, age, sex, and disease status of participants) of the included studies, no pooling of data, syntheses, or meta-analyses could be completed. It should be noted that there were no formal assessments of publication bias during the systematic literature review. However, a CASP checklist was completed for each included study, which deemed the research to be of sufficient quality for inclusion. Nonetheless, each study had limitations which should be considered when interpreting their results. The possibility of publication bias was not formally analysed.

Further pharmacoepidemiological studies are urgently needed to address many of the limitations of spontaneous reporting in understanding myocarditis and pericarditis following mRNA COVID-19 vaccines including more accurate estimates of the frequency, better understanding of the clinical course and the effects of these events on quality of life. It is also important to compare the incidence and characteristics of these events with recipients of other non-mRNA COVID-19 vaccines and unvaccinated people. However, these studies will take time to be conducted.

Conclusions

This study adds to existing evidence that younger vaccinees more frequently report myocarditis and pericarditis following mRNA COVID-19 vaccines compared with older vaccinees, and reports are more frequent following the second dose. These events are very rare or possibly rare according to the estimated reporting rates from spontaneous adverse reactions. The events were more frequently reported amongst males, and most reports came from vaccinees aged under 30 years. The clinical course of these events is typically mild, with full recovery in most cases.

The study brings together spontaneously reported adverse event data from three regions. Consistencies in the reporting rates and trends of myocarditis and pericarditis within the three data sources utilised suggest that results may be generalisable to other populations in which mRNA vaccines are used. However, limitations of the data sources used and biases which may have affected results should be considered. It is important that regulatory authorities continue to monitor the effects of mRNA vaccines on the heart, particularly as vaccine programmes progress to include younger vaccinees in many parts of the world. Myocarditis and pericarditis following mRNA COVID-19 vaccines is an area which requires further research, especially in children and adolescents and following third and subsequent (booster) doses. Pharmacoepidemiological studies are urgently needed to address many of the limitations of spontaneous reporting in understanding myocarditis and

pericarditis following mRNA COVID-19 vaccines including more accurate estimates of frequency, a better understanding of the clinical course, and the effects on quality of life. However, they will take time to be conducted. We believe that the data we describe here will enhance the understanding of these conditions and help with identification of potential sources of mechanisms of vaccine-associated myocarditis and pericarditis by identifying which populations are most likely to suffer these adverse events following COVID-19 mRNA vaccination.

Declarations

Transparency statement

The manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported, and that no important aspects of the study have been omitted.

Ethics approval

Ethics approval was not required.

Funding

No external funding was received for the preparation of this manuscript.

Competing interests

All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: The Drug Safety Research Unit (DSRU) is a registered independent charity (No. 327206) associated with the University of Portsmouth. The DSRU receives donations and grants from pharmaceutical companies; however, the companies have no control over the conduct or publication of its studies. The DSRU has received grants to conduct unconditional studies on the Oxford/AstraZeneca COVID-19 vaccine and is in negotiations to receiving grants for conducting CPRD studies for Pfizer, Moderna, and Janssen COVID-19 vaccines. The DSRU has conducted benefit-risk studies on products for COVID-19, including remdesivir, lopinavir/ritonavir, chloroquine and hydroxychloroquine, and convalescent plasma. Professor Shakir is the principal investigator for an active surveillance study for the Oxford/AstraZeneca vaccine, but this assessment is unrelated to this study. Professor Shakir has been a member of Data Safety Monitoring Boards for Ipsen, Biogen, and Diurnal. None of these companies have any involvement with COVID-19 vaccines. Professor Shakir was invited by AstraZeneca to advise on the events of thrombosis with thrombocytopenia with the COVID-19 vaccine and to be a member of an advisory committee on a safety study of the Oxford/AstraZeneca vaccine in Europe. Samantha Lane and Alison Yeomans have no conflicts of interest with regard to this study.

Contributors

SL and AY were responsible for data acquisition from the spontaneous reporting systems used in this study, conducted literature searches, critical appraisal of the literature, and subsequent data extraction, and conducted all data analyses. SS, SL and AY were responsible for study conception and planning, interpretation of the data, drafting and reviewing the manuscript, and approval of the final version for publication. SS was guarantor of this manuscript.

Data availability statement

No additional data are available.

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7.0 Figure Legends

Figure 1: Flowchart detailing inclusion of studies for systematic review
Literature searches were carried out in PubMed/MEDLINE and simultaneously in Embase. The identified records were de-duplicated prior to screening to remove duplicate publications. Records were then screened to remove literature that did not meet the search criteria and eligibility was assessed prior to inclusion into the literature review.

Figure 2: Event counts and reporting rates of myocarditis and pericarditis in the UK, US and EU
(A) Events of myocarditis and pericarditis reported to the Yellow Card scheme (UK), VAERS (US) and EudraVigilance (EU) reporting systems following any dose of COVID-19 mRNA vaccines separated by vaccine manufacturer combined to give total counts. (B) Reporting rates of myocarditis and pericarditis following any dose of COVID-19 mRNA vaccine separated by vaccine manufacturer and reporting region.

Figure 3: Myocarditis and pericarditis reports separated by gender
(A) Percentage of males and females experiencing myocarditis and pericarditis reported to each reporting system (Yellow Card, VAERS and EudraVigilance). Bars represent the total of all myocarditis and pericarditis reports to each system, separated by gender, where bars do not meet 100% indicates reports where gender was not specified. Values indicate the percentage of males experiencing these events. (B) Reports in each region were stratified by vaccine manufacturer as well as gender experiencing these events. Stacked bars represent the total number of reports, where gender was specified, from each region for each vaccine type. Values depict the percentage of males that experienced these events.

Figure 4: Myocarditis and pericarditis events following COVID-19 mRNA vaccination separated by dose
Data from the VAERS (US) reporting system was separated by reaction type; myocarditis (A) and pericarditis (B), vaccine manufacturer and by dose received. Stacked bars represent the male and female reports of each condition according to the dose received.

Table 1: Reports of myocarditis and pericarditis submitted to Yellow Card scheme, by age and sex

Datalock point 16 March 2022.

	Comirnaty		Spikevax		Total	
	n	%	n	%	n	%
Age group (years						
<18 Years	70	5.68	0	0.00	70	4.50
18-29 Years	372	30.19	114	35.19	486	31.23
30-39 Years	299	24.27	92	28.40	391	25.13
40-49 Years	137	11.12	48	14.81	185	11.89
50-59 Years	92	7.47	22	6.79	114	7.33
60+ Years	146	11.85	15	4.63	161	10.35
Age not specified	144	11.69	34	10.49	178	11.44
Sex						
Female	492	39.94	109	33.64	601	38.62
Male	731	59.33	206	63.58	937	60.22
Sex not specified	37	3.00	10	3.09	47	3.02
Total	1260	100.00	325	100.00	**1585**	**100.00**

Table 2: Myocarditis and pericarditis events reported to VAERS overall

Datalock point 14 March 2022. Percentages per age group are presented.

Age Group	Myocarditis								Pericarditis							
	Male		Female		Sex Not Specified		Total		Male		Female		Sex Not Specified		Total	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	N	%
Comirnaty (PfizerBioNTech)																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.23	0	0.00	1	0.09
3-5 Years	2	0.15	0	0.00	0	0.00	2	0.11	1	0.14	0	0.00	0	0.00	1	0.09
6-17 Years	525	38.80	67	15.44	2	5.41	594	32.57	145	20.14	23	5.32	1	10.00	169	14.54
18-29 Years	404	29.86	102	23.50	1	2.70	507	27.80	217	30.14	51	11.81	0	0.00	268	23.06
30-39 Years	157	11.60	69	15.90	2	5.41	228	12.50	116	16.11	78	18.06	0	0.00	194	16.70
40-49 Years	68	5.03	59	13.59	0	0.00	127	6.96	56	7.78	83	19.21	0	0.00	139	11.96
50-59 Years	41	3.03	56	12.90	0	0.00	97	5.32	64	8.89	73	16.90	0	0.00	137	11.79
60-64 Years	13	0.96	21	4.84	2	5.41	36	1.97	20	2.78	43	9.95	0	0.00	63	5.42
65-79 Years	52	3.84	31	7.14	2	5.41	85	4.66	67	9.31	50	11.57	2	20.00	119	10.24
80+ Years	5	0.37	4	0.92	0	0.00	9	0.49	12	1.67	9	2.08	0	0.00	21	1.81
Not Specified	86	6.36	25	5.76	28	75.68	139	7.62	22	3.06	21	4.86	7	70.00	50	4.30
Total	1353	100.00	434	100.00	37	100.00	**1824**	100.00	720	100.00	432	100.00	10	100.00	**1162**	100.00
Spikevax (Moderna)																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	5	0.78	1	0.37	2	10.53	8	0.86	1	0.26	0	0.00	0	0.00	1	0.14
18-29 Years	317	49.15	64	23.79	1	5.26	382	40.94	130	33.33	62	20.39	0	0.00	192	27.16
30-39 Years	135	20.93	51	18.96	0	0.00	186	19.94	59	15.13	38	12.50	1	7.69	98	13.86
40-49 Years	62	9.61	51	18.96	0	0.00	113	12.11	57	14.62	54	17.76	0	0.00	111	15.70

50-59 Years	41	6.36	37	13.75	1	5.26	79	8.47	52	13.33	52	17.11	0	0.00	104	14.71
60-64 Years	15	2.33	24	8.92	0	0.00	39	4.18	24	6.15	31	10.20	1	7.69	56	7.92
65-79 Years	29	4.50	35	13.01	0	0.00	64	6.86	54	13.85	53	17.43	2	15.38	109	15.42
80+ Years	5	0.78	4	1.49	0	0.00	9	0.96	6	1.54	11	3.62	0	0.00	17	2.40
Not Specified	36	5.58	2	0.74	15	78.95	53	5.68	7	1.79	3	0.99	9	69.23	19	2.69
Total	645	100.00	269	100.00	19	100.00	**933**	100.00	390	100.00	304	100.00	13	100.00	**707**	100.00
Overall (both mRNA vaccines)																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.14	0	0.00	1	0.05
3-5 Years	2	0.10	0	0.00	0	0.00	2	0.07	1	0.09	0	0.00	0	0.00	1	0.05
6-17 Years	530	26.53	68	9.67	4	7.14	602	21.84	146	13.15	23	3.13	1	4.35	170	9.10
18-29 Years	721	36.09	166	23.61	2	3.57	889	32.25	347	31.26	113	15.35	0	0.00	460	24.61
30-39 Years	292	14.61	120	17.07	2	3.57	414	15.02	175	15.77	116	15.76	1	4.35	292	15.62
40-49 Years	130	6.51	110	15.65	0	0.00	240	8.71	113	10.18	137	18.61	0	0.00	250	13.38
50-59 Years	82	4.10	93	13.23	1	1.79	176	6.38	116	10.45	125	16.98	0	0.00	241	12.89
60-64 Years	28	1.40	45	6.40	2	3.57	75	2.72	44	3.96	74	10.05	1	4.35	119	6.37
65-79 Years	81	4.05	66	9.39	2	3.57	149	5.40	121	10.90	103	13.99	4	17.39	228	12.20
80+ Years	10	0.50	8	1.14	0	0.00	18	0.65	18	1.62	20	2.72	0	0.00	38	2.03
Not Specified	122	6.11	27	3.84	43	76.79	192	6.96	29	2.61	24	3.26	16	69.57	69	3.69
Total	1998	100.00	703	100.00	56	100.00	2757	100.00	1110	100.00	736	100.00	23	100.00	1869	100.00
Grand Total	**1998**	**72.47**	**703**	**25.50**	**56**	**2.03**	**2757**	**100.00**	**1110**	**59.39**	**736**	**39.38**	**23**	**1.23**	**1869**	**100.00**

Table 3: Myocarditis and pericarditis events reported to EudraVigilance for the European Economic Area
Datalock point 14 March 2022. Percentages per age group are presented.

Age Group	Myocarditis								Pericarditis							
	Male		Female		Sex Not Specified		Total		Male		Female		Sex Not Specified		Total	
	n	%	n	%	n	%	N	%	n	%	n	%	n	%	N	%
Comirnaty (Pfizer/BioNTech)																
2 Months-2 Years	0	0.00	0	0.00	0	0.00	0	0.00	67	63.81	38	36.19	0	0.00	105	100.00
3-11 Years	4	66.67	2	33.33	0	0.00	6	100.00	798	48.33	848	51.36	5	0.30	1651	100.00
12-17 Years	507	86.82	72	12.33	5	0.86	584	100.00	164	56.75	125	43.25	0	0.00	289	100.00
18-64 Years	2302	70.16	956	29.14	23	0.70	3281	100.00	307	46.30	351	52.94	5	0.75	663	100.00
65-85 Years	130	50.58	125	48.64	2	0.78	257	100.00	54	46.55	62	53.45	0	0.00	116	100.00
85+ Years	12	52.17	11	47.83	0	0.00	23	100.00	1042	50.27	1026	49.49	5	0.24	2073	100.00
Not Specified	86	60.56	39	27.46	17	11.97	142	100.00	8	38.10	11	52.38	2	9.52	21	100.00
Total	3041	70.84	1205	28.07	47	1.09	**4293**	**100.00**	2440	49.61	2461	50.04	17	0.35	**4918**	**100.00**
Spikevax (Moderna)																
2 Months-2 Years	0	0.00	0	0.00	0	0.00	0	0.00	8	0.00	4	0.00	0	0.00	12	100.00
3-11 Years	0	0.00	0	0.00	0	0.00	0	0.00	343	0.00	287	0.00	5	0.79	635	100.00
12-17 Years	69	92.00	6	8.00	0	0.00	75	100.00	39	0.00	45	0.00	0	0.00	84	100.00
18-64 Years	913	79.39	231	20.09	6	0.52	1150	100.00	0	0.00	2	100.00	0	0.00	2	100.00
65-85 Years	27	48.21	29	51.79	0	0.00	56	100.00	4	50.00	4	50.00	0	0.00	8	100.00
85+ Years	1	33.33	2	66.67	0	0.00	3	100.00	394	53.17	342	46.15	5	0.67	741	100.00

Not Specified	11	55.00	7	35.00	2	10.00	20	100.00	0	0.00	0	0.00	0	0.00	0	-
Total	1021	78.30	275	21.09	8	0.61	**1304**	**100.00**	788	53.17	684	46.15	10	0.67	**1482**	**100.00**
Overall (both mRNA vaccines)																
2 Months-2 Years	0	0.00	0	0.00	0	0.00	0	-	75	64.10	42	35.90	0	0.00	117	100.00
3-11 Years	4	66.67	2	33.33	0	0.00	6	100.00	1141	49.91	1135	49.65	10	0.44	2286	100.00
12-17 Years	576	87.41	78	11.84	5	0.76	659	100.00	203	54.42	170	45.58	0	0.00	373	100.00
18-64 Years	3215	72.56	1187	26.79	29	0.65	4431	100.00	307	46.17	353	53.08	5	0.75	665	100.00
65-85 Years	157	50.16	154	49.20	2	0.64	313	100.00	58	46.77	66	53.23	0	0.00	124	100.00
85+ Years	13	50.00	13	50.00	0	0.00	26	100.00	1436	51.03	1368	48.61	10	0.36	2814	100.00
Not Specified	97	59.88	46	28.40	19	11.73	162	100.00	8	38.10	11	52.38	2	9.52	21	100.00
Total	4058	72.55	1480	26.46	55	0.98	**5593**	**100.00**	3228	50.44	3145	49.14	27	0.42	**6400**	**100.00**

Table 4: Results of studies identified by systematic review, including the number of events, fatal cases, sex, and vaccine dose

	Myocarditis		Myopericarditis		Pericarditis		Total cases		Fatal cases		Males (where specified)		Females (where specified)		Single dose		Two doses		Dose unspecified	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	N	%	n	%
1	21	43.75	27	56.25	0	0.00	48	100.00	NR		NR		NR		NR		NR		NR	
2	1241	54.94	851	37.67	167	7.39	2259	100.00	22	45.83	1555	68.84	722	31.96	NR		NR		NR	
3	33	100.00	0	0.00	0	0.00	33	100.00	NR		29	87.88	4	12.12	6	18.18	27	81.82	0	0
4	20	36.36	0	0.00	35	63.64	55	100.00	NR		42	76.36	15	27.27	NR		NR		NR	
5	0	0.00	4	100.00	0	0.00	4	100.00	NR		2	50	2	50	3	75	1	25	0	0
6	0	0.00	10	100.00	0	0.00	10	100.00	NR		6	60	6	60	3	30	7	70	0	0
7	191	78.93	2	0.83	49	20.25	242	100.00	1	0.41	205	84.71	37	15.29	37	15.29	68	28.1	139	57.44
8	21	100.00	0	0.00	0	0.00	21	100.00	NR		17	80.95	4	19.05	NR		NR		NR	
9	1226	100.00	0	0.00	0	0.00	1226	100.00	0	0.00	923	75.29	289	23.57	263	21.45	831	67.78	0	0
10	0	0.00	12	100.00	0	0.00	12	100.00	0	0.00	NR		NR		NR		NR		NR	
11	1579	59.77	0	0.00	1063	40.23	2642	100.00	NR		1906	72.14	736	27.86	NR		NR		NR	
12	397	100.00	0	0.00	0	0.00	397	100.00	0	0.00	NR		NR		NR		NR		NR	
13	48	69.57	21	30.43	0	0.00	69	100.00	NR		NR		NR		NR		NR		NR	
14	63	100.00	0	0.00	0	0.00	63	100.00	NR		58	92.06	5	7.94	1	1.59	62	98.41	0	0
15	156	100.00	0	0.00	0	0.00	156	100.00	5	3.21	131	83.97	74	47.44	NR		NR		NR	
16	0	0.00	34	100.00	0	0.00	34	100.00	NR		29	85.29	5	14.71	9	26.47	24	70.59	1	2.94
17	0	0.00	20	100.00	0	0.00	20	100.00	1	5.00	15	75	6	30	13	65	7	35	0	0
18	20	100.00	0	0.00	0	0.00	20	100.00	NR		12	60	8	40	5	25	15	75	0	0
19	0	0.00	20	100.00	0	0.00	20	100.00	NR		NR		NR		NR		NR		NR	
20	0	0.00	2038	100.00	0	0.00	2038	100.00	NR		1474	72.33	535	26.25	NR		NR		NR	
21	43	100.00	0	0.00	0	0.00	43	100.00	NR		38	88.37	5	11.63	7	16.28	36	83.72	0	0
22	182	100.00	0	0.00	0	0.00	182	100.00	1	0.55	NR		NR		0	0	142	78.02	40	21.98
23	0	0.00	12	80.00	3	20.00	15	100.00	0	0.00	13	86.67	2	13.33	8	53.33	7	46.67	0	0

24	4	100.00	0	0.00	0	0.00	4	100.00	0	0.00	4	100	0	0	2	50	2	50	0	0
25	1625	70.38	0	0.00	684	29.62	2309	100.00	0	0.00	1334	57.77	290	12.56	273	11.82	1265	54.79	0	0
26	158	54.11	0	0.00	134	45.89	292	100.00	NR		173	59.25	119	40.75	153	52.4	139	47.6	0	0
27	0	0.00	1072	100.00	0	0.00	1072	100.00	NR		NR		NR		NR		NR		NR	
28	15	100.00	0	0.00	0	0.00	15	100.00	NR		15	100	0	0	2	13.33	13	86.67	0	0
29	146	100.00	0	0.00	0	0.00	146	100.00	NR		126	86.3	20	13.7	12	8.22	134	91.78	0	0
30	38	100.00	0	0.00	0	0.00	38	100.00	NR		NR		NR		8	21.05	30	78.95	0	0
31	54	100.00	0	0.00	0	0.00	54	100.00	NR		51	94.44	3	5.56	17	31.48	37	68.52	0	0
32	14	41.18	11	32.35	9	26.47	34	100.00	0	0.00	28	82.35	6	17.65	15	44.12	19	55.88	0	0
Total	7295		4134		2144		13573		30		8186		2893		837		2866		180	
Average (%)		59.66		32.42		7.92		100.00		4.58		78.33		22.86		29.00		64.72		4.12

Table 5: Myocarditis and pericarditis events reported to VAERS following Pfizer/BioNTech COVID-19 vaccine (Comirnaty), by dose

Datalock point 14 March 2022. Percentages per age group are presented.

Age Group	Myocarditis								Pericarditis							
	Male		Female		Sex Not Specified		Total		Male		Female		Sex Not Specified		Total	
	n	%	n	%	n	%	N	%	n	%	n	%	N	%	N	%
Dose 1																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	1	0.53	0	0.00	0	0.00	1	0.30
6-17 Years	95	37.55	13	10.24	0	0.00	108	28.20	28	14.81	10	7.09	0	0.00	38	11.48
18-29 Years	69	27.27	23	18.11	0	0.00	92	24.02	56	29.63	21	14.89	0	0.00	77	23.26
30-39 years	37	14.62	28	22.05	1	33.33	66	17.23	38	20.11	26	18.44	0	0.00	64	19.34
40-49 years	15	5.93	18	14.17	0	0.00	33	8.62	12	6.35	23	16.31	0	0.00	35	10.57
50-59 years	8	3.16	19	14.96	0	0.00	27	7.05	21	11.11	27	19.15	0	0.00	48	14.50
60-64 years	3	1.19	8	6.30	0	0.00	11	2.87	6	3.17	15	10.64	0	0.00	21	6.34
65-79 Years	14	5.53	10	7.87	0	0.00	24	6.27	22	11.64	13	9.22	0	0.00	35	10.57
80+ Years	0	0.00	3	2.36	0	0.00	3	0.78	3	1.59	2	1.42	0	0.00	5	1.51
Not Specified	12	4.74	5	3.94	2	66.67	19	4.96	2	1.06	4	2.84	1	100.00	7	2.11
Total	253	100.00	127	100.00	3	100.00	**383**	**100.00**	189	100.00	141	100.00	1	100.00	**331**	**100.00**
Dose 2																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	1	0.59	0	0.00	1	0.19
3-5 Years	2	0.27	0	0.00	0	0.00	2	0.21	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	305	40.99	37	18.05	1	14.29	343	35.88	83	23.12	11	6.51	0	0.00	94	17.67
18-29 Years	210	28.23	47	22.93	1	14.29	258	26.99	105	29.25	15	8.88	0	0.00	120	22.56
30-39 years	84	11.29	34	16.59	0	0.00	118	12.34	62	17.27	32	18.93	0	0.00	94	17.67
40-49 years	41	5.51	29	14.15	0	0.00	70	7.32	27	7.52	30	17.75	0	0.00	57	10.71

50-59 years	17	2.28	26	12.68	0	0.00	43	4.50	32	8.91	31	18.34	0	0.00	63	11.84
60-64 years	6	0.81	6	2.93	0	0.00	12	1.26	7	1.95	17	10.06	0	0.00	24	4.51
65-79 Years	21	2.82	14	6.83	0	0.00	35	3.66	28	7.80	19	11.24	1	25.00	48	9.02
80+ Years	3	0.40	0	0.00	0	0.00	3	0.31	6	1.67	3	1.78	0	0.00	9	1.69
Not Specified	55	7.39	12	5.85	5	71.43	72	7.53	9	2.51	10	5.92	3	75.00	22	4.14
Total	744	100.00	205	100.00	7	100.00	**956**	**100.00**	359	100.00	169	100.00	4	100.00	**532**	**100.00**
Dose 3																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	34	32.08	4	12.12	0	0.00	38	26.57	10	18.87	0	0.00	0	0.00	10	9.01
18-29 Years	29	27.36	9	27.27	0	0.00	38	26.57	10	18.87	5	8.93	0	0.00	15	13.51
30-39 years	13	12.26	4	12.12	0	0.00	17	11.89	5	9.43	13	23.21	0	0.00	18	16.22
40-49 years	2	1.89	5	15.15	0	0.00	7	4.90	7	13.21	17	30.36	0	0.00	24	21.62
50-59 years	7	6.60	4	12.12	0	0.00	11	7.69	4	7.55	7	12.50	0	0.00	11	9.91
60-64 years	2	1.89	3	9.09	0	0.00	5	3.50	1	1.89	6	10.71	0	0.00	7	6.31
65-79 Years	12	11.32	3	9.09	2	50.00	17	11.89	11	20.75	5	8.93	1	50.00	17	15.32
80+ Years	2	1.89	0	0.00	0	0.00	2	1.40	3	5.66	1	1.79	0	0.00	4	3.60
Not Specified	5	4.72	1	3.03	2	50.00	8	5.59	2	3.77	2	3.57	1	50.00	5	4.50
Total	106	100.00	33	100.00	4	100.00	**143**	**100.00**	53	100.00	56	100.00	2	100.00	**111**	**100.00**
Dose 4+																
60-64 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	100.00	0	0.00	2	100.00
Total	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	100.00	0	0.00	2	100.00
Unknown dose																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	91	36.40	13	18.84	1	4.35	105	30.70	24	20.17	2	3.13	1	25.00	27	14.44

18-29 Years	96	38.40	23	33.33	0	0.00	119	34.80	46	38.66	10	15.63	0	0.00	56	29.95
30-39 years	23	9.20	3	4.35	1	4.35	27	7.89	11	9.24	7	10.94	0	0.00	18	9.63
40-49 years	10	4.00	7	10.14	0	0.00	17	4.97	10	8.40	13	20.31	0	0.00	23	12.30
50-59 years	9	3.60	7	10.14	0	0.00	16	4.68	7	5.88	8	12.50	0	0.00	15	8.02
60-64 years	2	0.80	4	5.80	2	8.70	8	2.34	6	5.04	3	4.69	0	0.00	9	4.81
65-79 Years	5	2.00	4	5.80	0	0.00	9	2.63	6	5.04	13	20.31	1	25.00	20	10.70
80+ Years	0	0.00	1	1.45	0	0.00	1	0.29	0	0.00	3	4.69	0	0.00	3	1.60
Not Specified	14	5.60	7	10.14	19	82.61	40	11.70	9	7.56	5	7.81	2	50.00	16	8.56
Total	250	100.00	69	100.00	23	100.00	342	100.00	119	100.00	64	100.00	4	100.00	187	100.00
Grand Total	1353		434		37		**1824**		720		432		11		**1162**	

Table 6: Myocarditis and pericarditis events reported to VAERS following Moderna COVID-19 vaccine (Spikevax), by dose

Datalock point 14 March 2022. Percentages per age group are presented

Age Group	Myocarditis								Pericarditis							
	Male		Female		Sex Not Specified		Total		Male		Female		Sex Not Specified		Total	
	n	%	n	%	n	%	N	%	n	%	n	%	N	%	N	%
Dose 1																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	1	0.56	0	0.00	0	0.00	1	0.35	0	0.00	0	0.00	0	0.00	0	0.00
18-29 Years	74	41.11	18	18.00	0	0.00	92	32.17	33	32.35	23	20.00	0	0.00	56	25.23
30-39 years	42	23.33	18	18.00	0	0.00	60	20.98	15	14.71	17	14.78	0	0.00	32	14.41
40-49 years	16	8.89	21	21.00	0	0.00	37	12.94	21	20.59	20	17.39	0	0.00	41	18.47
50-59 years	15	8.33	16	16.00	1	16.67	32	11.19	12	11.76	19	16.52	0	0.00	31	13.96
60-64 years	3	1.67	15	15.00	0	0.00	18	6.29	7	6.86	12	10.43	0	0.00	19	8.56
65-79 Years	10	5.56	11	11.00	0	0.00	21	7.34	11	10.78	16	13.91	2	40.00	29	13.06
80+ Years	2	1.11	1	1.00	0	0.00	3	1.05	0	0.00	5	4.35	0	0.00	5	2.25
Not Specified	17	9.44	0	0.00	5	83.33	22	7.69	3	2.94	3	2.61	3	60.00	9	4.05
Total	180	100.00	100	100.00	6	100.00	286	100.00	102	100.00	115	100.00	5	100.00	222	100.00
Dose 2																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	2	0.72	0	0.00	0	0.00	2	0.52	1	0.55	0	0.00	0	0.00	1	0.33
18-29 Years	152	54.48	29	29.00	1	20.00	182	47.40	63	34.81	24	19.67	0	0.00	87	28.52
30-39 years	57	20.43	15	15.00	0	0.00	72	18.75	30	16.57	11	9.02	0	0.00	41	13.44
40-49 years	24	8.60	24	24.00	0	0.00	48	12.50	20	11.05	21	17.21	0	0.00	41	13.44
50-59 years	20	7.17	13	13.00	0	0.00	33	8.59	25	13.81	24	19.67	0	0.00	49	16.07

60-64 years	6	2.15	5	5.00	0	0.00	11	2.86	10	5.52	12	9.84	0	0.00	22	7.21
65-79 Years	13	4.66	12	12.00	0	0.00	25	6.51	26	14.36	26	21.31	0	0.00	52	17.05
80+ Years	1	0.36	1	1.00	0	0.00	2	0.52	4	2.21	4	3.28	0	0.00	8	2.62
Not Specified	4	1.43	1	1.00	4	80.00	9	2.34	2	1.10	0	0.00	2	100.00	4	1.31
Total	279	100.00	100	100.00	5	100.00	**384**	**100.00**	181	100.00	122	100.00	2	100.00	**305**	**100.00**
Dose 3																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	1	1.96	0	0.00	0	0.00	1	1.16	0	0.00	0	0.00	0	0.00	0	0.00
18-29 Years	29	56.86	8	22.86	0	0.00	37	43.02	10	29.41	6	16.22	0	0.00	16	22.54
30-39 years	9	17.65	10	28.57	0	0.00	19	22.09	4	11.76	7	18.92	0	0.00	11	15.49
40-49 years	6	11.76	4	11.43	0	0.00	10	11.63	5	14.71	8	21.62	0	0.00	13	18.31
50-59 years	2	3.92	4	11.43	0	0.00	6	6.98	7	20.59	5	13.51	0	0.00	12	16.90
60-64 years	1	1.96	2	5.71	0	0.00	3	3.49	1	2.94	3	8.11	0	0.00	4	5.63
65-79 Years	3	5.88	6	17.14	0	0.00	9	10.47	6	17.65	6	16.22	0	0.00	12	16.90
80+ Years	0	0.00	1	2.86	0	0.00	1	1.16	1	2.94	2	5.41	0	0.00	3	4.23
Not Specified	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total	51	100.00	35	100.00	0	0.00	86	100.00	34	100.00	37	100.00	0	0.00	71	100.00
Dose 4+																
40-49 Years	0	0.00	1	100.00	0	0.00	1	100.00	0	0.00	0	0.00	0	0.00	0	0.00
Total	0	0.00	1	100.00	0	0.00	1	100.00	0	0.00	0	0.00	0	0.00	0	0.00
Unknown dose																
<6 months	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
3-5 Years	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
6-17 Years	1	0.74	1	3.03	2	25.00	4	2.27	0	0.00	0	0.00	0	0.00	0	0.00
18-29 Years	62	45.93	9	27.27	0	0.00	71	40.34	24	32.88	9	30.00	0	0.00	33	30.28
30-39 years	27	20.00	8	24.24	0	0.00	35	19.89	10	13.70	3	10.00	1	16.67	14	12.84

40-49 years	16	11.85	1	3.03	0	0.00	17	9.66	11	15.07	5	16.67	0	0.00	16	14.68
50-59 years	4	2.96	4	12.12	0	0.00	8	4.55	8	10.96	4	13.33	0	0.00	12	11.01
60-64 years	5	3.70	2	6.06	0	0.00	7	3.98	6	8.22	4	13.33	1	16.67	11	10.09
65-79 Years	3	2.22	6	18.18	0	0.00	9	5.11	11	15.07	5	16.67	0	0.00	16	14.68
80+ Years	2	1.48	1	3.03	0	0.00	3	1.70	1	1.37	0	0.00	0	0.00	1	0.92
Not Specified	15	11.11	1	3.03	6	75.00	22	12.50	2	2.74	0	0.00	4	66.67	6	5.50
Total	135	100.00	33	100.00	8	100.00	176	100.00	73	100.00	30	100.00	6	100.00	109	100.00
Grand Total	645		269		19		**933**		390		304		13		**707**	

Table 7: Details of each study identified by systematic review which met the inclusion criteria

	First author & citation	Study design	Study period	Vaccine	Population	No. cases in exposed to mRNA vaccine	Diagnostic criteria	Percentage of cases who were male	Age of cases	Vaccine dose	RR (95% CI)	Incidence (95% CI)
1	Barda (48)	Cohort with unvaccinated comparator	December 2020 - May 2021	Comirnaty	Israel, electronic health records	Myocarditis n=21; Pericarditis n=27		NR	NR	NR	Myocarditis = 3.24 (1.55 to 12.44); Pericarditis = 1.27 (0.68 to 2.31)	NC
2	Chouchana (25)	Analysis of VigiBase spontaneous reports	Vaccine launch - end June 2021	mRNA COVID vaccine	Vigibase reports	Myocarditis n=1241; Pericarditis n=851; Myo-pericarditis n=167; Pleuro-pericarditis n=18		68.30%	Median 33 (21–54) years	NR	NC	NC
3	Chua (49)	Population cohort study	14 June 2021 - 4 September 2021	Comirnaty	Hong Kong adolescents, electronic health records	n=33 cases (myocarditis/ pericarditis)		87.88%	Median 15.25 years	81.82% followed 2nd dose	NC	Overall = 18.52 (95% CI 11.67–29.01); Males = 32.29 (95% CI 22.78–45.4); Females = 4.53 (95% CI 1.76–11.11)
4	Das (50)	Cross sectional study of 25 children aged 12-18 years diagnosed with probable myopericarditis following COVID-19 mRNA vaccination	10 May 2021 - 20 June 2021	Comirnaty	Adolescents presenting at 8 US centres	n=25 (myo-pericarditis)		88%	Range 12-17 years	88% followed 2nd dose	NC	NC

5	Diaz (51)	Retrospective cohort	Vaccine launch - 25 May 2021	mrNA COVID vaccine plus AZ vaccine	40 US hospitals, electronic health records	Myocarditis n=20; pericarditis n=35	Myocarditis75%; pericarditis 73%	Myocarditis cases median 36 (26.3-48.3) years; Pericarditis cases median 59 (46-69) years	NR	NC	NC
6	Eggebrecht (52)	Cohort	27 December 2020 - 3 September 2021	All COVID vaccines	113 patients at cardiology unit	Comirnaty cases n=85; Spikevax n=13	56%	Average age 45.9 years, 95% CI 43.2–48.7	57% followed 2nd dose	NC	NC
7	Farahmand (26)	Cohort	3 August 2020 – 21 May 2021	All COVID vaccines	Patients and employees of the Beth Israel Deaconess Medical Center (BIDMC), electronic health records	n=7	50.00%	Participants aged 25 years and older	NR	Age adjusted rate ratio = 9.7 (p=0.04)	NC
8	Foltran (53)	Analysis of VigiBase spontaneous reports	1 January - 14 September 2021	mRNA COVID vaccines	Vigibase reports for adolescents aged 12-17 years	n=242 cases (pericarditis and/or myocarditis)	85%	Mean 15.8 (+/- 1.4yrs)	1 or 2 doses	NC	NC
9	Fronza (54)	Retrospective cohort	December 2019 – November 2021	All COVID vaccines	Consecutive adults referred to a tertiary hospital network for MRI	Spikevax n=12; Comirnaty n=9	81%	Mean (SD) 31 (14) years	17 followed 2nd dose	NC	NC
10	Gargano (55)	Analysis of VAERS spontaneous reports	29 December 2020 – 11 June 2021	mRNA COVID vaccines	VAERS reports	n=1226	76.2% of 1212 cases where sex available	Median age 26 years (range 12–94 years)	76% followed 2nd dose (where dose was reported)	NC	NC
11	Golino (56)	Observational study	June - August 2021	mRNA COVID vaccines	Hospital admissions, University of Insubria, Varese, Italy	n=12 (myo-pericarditis)	33% of cases were young males	Males aged 29 (+/- 12) years	NR	NC	NC
12	Hajjo (39)	VAERS analysis	Vaccine launch – 2 September 2021	All COVID vaccines	VAERS reports	Myocarditis = 1579; Pericarditis = 1063	myo = 77%, peri = 65%	Range 6-80+ years	1-3 doses	NC	NC

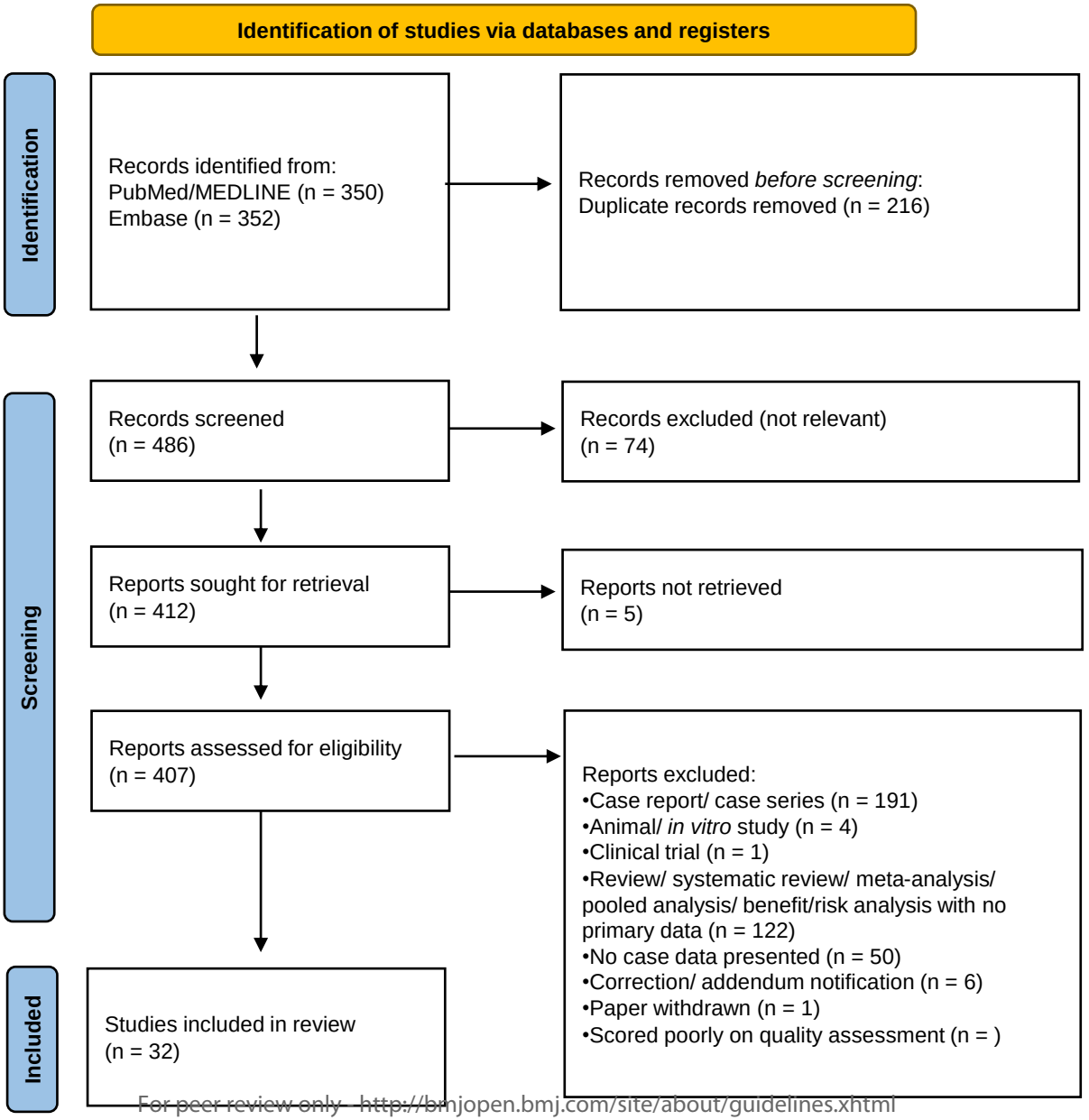
13	Hause (12)	VAERS & V-Safe analysis	14 December 2020 – 16 July 2021	Comirnaty	VAERS and V-Safe reports for adolescents	n=379 (myocarditis)	NR	NR	NR	NC	NC
14	Husby (57)	Population-based cohort study	1 October 2020 – 5 October 2021	All COVID vaccines	Danish health records databases (all individuals in Denmark aged 12 and over)	Comirnaty n=48; Spikevax n=21	NR	NR	NR	NC	Absolute rate within 28 days of vaccination: Overall = 1.7 (95% CI 1.3 to 2.2) per 100,000 vaccinated individuals. Comirnaty = 1.4 (1.0 to 1.8) per 100,000 Spikevax = 4.2 (2.6 to 6.4) per 100,000
15	Jain (27)	Retrospective multicentre study	March 2021 – June 2021	mRNA COVID vaccines	Patients <21 years presenting to 16 US hospitals	Comirnaty n=59; Spikevax n=4	92%	Mean 15.6 ± 1.8 years (range 12 – 20 years)	62 cases followed 2nd dose	NC	NC
16	Kerneis (58)	Vigibase analysis	1967 – 7 May 2021	All COVID vaccines	Vigibase reports	Comirnaty n=151; Spikevax n=51	63.90%	Median 35 (IQR 25-50) years	NR	NC	NC
17	Klein (28)	Vaccine Safety Datalink analysis	14 December 2020 – 26 June 2021	mRNA COVID vaccines	Electronic health records	n=87 (myocarditis/ pericarditis)	85%	Range 12-39 years	NR	NC	NC
18	Knowlton (59)	Cohort / Case-crossover	15 December 2020 – 15 June 2021	All COVID vaccines	Adult patients presenting at Intermountain Healthcare	Comirnaty n=5; Spikevax n=15	71.40%	Median (IQR) 56 (28-70) years	NR	Within 60 days RR = 1.63 (95% CI 0.95-2.71); Within 30 days RR=2.05 (95% CI 1.17-3.48)	NC
19	Kravchenko (60)	Retrospective cohort	NR	mRNA COVID-19 vaccines	All patients referred for cardiac MRI to the Department of Diagnostic and Interventional Radiology,	Comirnaty n=19; Spikevax n=1	60%	Mean age 28 ± 12 years	75% followed 2nd dose	NC	NC

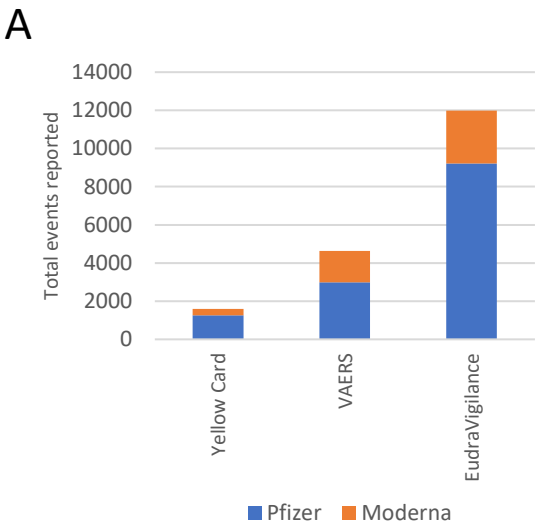
					University Hospital Bonn						
20	Lai (61)	Case-control	23 February – 2 August 2021	Comirnaty and Sinovac CoronaVac	Patients aged 12 and over, electronic health records provided by the Hospital Authority (HA) of Hong Kong; linked with population-based vaccination records	Comirnaty n=20	62.5% of 160 carditis cases overall	Mean (SD) age 57.48 (24.23) years overall for vaccinated and unvaccinated participants	13.1% followed 2nd dose	Carditis aOR= 3.57 (95% CI 1.93 - 6.60)	NC
21	Li (49)	VAERS analysis	11 December 2020 – 13 August 2021	All COVID vaccines	VAERS reports	Comirnaty n=1335 cases; Spikevax n=703	Spikevax = 69.6%, Comirnaty = 73.8%	Spikevax recipients aged 18 and older, Comirnaty recipients aged 12 and older	63.47% followed 2nd dose	NC	Incidence rate = 5.98 (95% CI = 5.73–6.24) cases per million doses administered
22	Li (29)	Cohort	10 March – 18 October 2021	Comirnaty	Hong Kong adolescents, electronic health records	n=43 (myocarditis)	88%	Mean (SD) 14.86 (1.46) years	84% followed 2nd dose	NC	NC
23	Mevorach (62)	Retrospective cohort	20 December 2020 – 31 May 2021	Comirnaty	Medical records, Ministry of Health database (Israel)	n=142 (myocarditis)	91% of the 95 cases for whom age and sex were available	16 years and older	91% followed 2nd dose	Rate Ratio=2.35 (95% CI, 1.10 to 5.02)	NC
24	Nygaard (63)	Prospective nationwide population-based cohort study	15 May 2021 – 15 September 2021	mRNA COVID vaccines	Hospitalised adolescents	Comirnaty n=15	87%	Range 13-17 years	47% after 2nd dose	NC	Males: 97 per million Females: 16 per million
25	Oh (64)	Retrospective observational study	1 June 2021 – 15 October 2021	mRNA COVID vaccines	Patients presenting at the Incheon and Daejeon hospitals' emergency departments	n=4 (myocarditis)	100%	Range 17-49 years	50% after 2nd dose	NC	NC
26	Oster (65)	VAERS analysis	December 2020 – August 2021	mRNA COVID vaccines	VAERS reports	n=1626 (myocarditis)	82%	Median = 21 years (IQR 16-31)	82% after 2nd dose	NC	NC

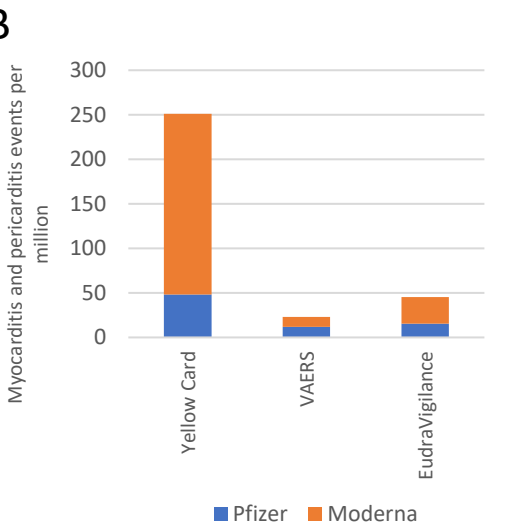
27	Patone (66)	Population-based cohort study	NR	Comirnaty or AZ	England	Myocarditis n=397; Pericarditis n=356	Myocarditis = 50% following 1st dose, 57.8% following 2nd dose; Pericarditis = 62.7% following 1st dose, 69.3% following 2nd dose	Myocarditis 1st dose mean (SD) 55.2 (22.0) years, myocarditis 2nd dose mean (SD) 61 (22.8) years; Pericarditis 1st dose mean (SD) 57.6 (20.1) years, Pericarditis 2nd dose mean (SD) 63.2 (18.7) years	52.1% received 1st dose only	Myocarditis 1st dose IRR=1.31 (95% CI 1.03 - 1.66); Myocarditis 2nd dose IRR=1.30 (95% CI 0.98 - 1.72); Pericarditis - No association	NC
28	Sa (67)	observational study (VAERS)	14th Dec 2020 – 30th Sept 2021	Comirnaty Spikevax or Janssen	US population, aged over 18yrs	Comirnaty n=1072; Spikevax n=791	NR	n=1573 18-64 years, n=193 65 years and older	NR	NC	NC
29	Simone (68)	retrospective population-based cohort study	14 December 2020 – 20 July 2021	mRNA COVID vaccines	Kaiser Permanente Southern California (KPSC) members aged 18 years and older	n=15 (myocarditis)	100%	Median (IQR) 52 (32-59) years	86.7% followed 2nd dose	1st dose: RR=0.38 (95%CI 0.05-1.40) 2nd dose: RR=2.7 (95% CI 1.4-4.8)	NC
30	Truong (69)	Retrospective cohort	Until 4 July 2021	All COVID vaccines	adolescents and young adults <21 years old, presenting at 26 paediatric medical centres across US and Canada	Comirnaty n=131, Spikevax n=5	90.60%	Median 15.8 (range 12.1-20.3) years	91.4% followed 2nd dose	NC	NC
31	Tsun Lai (70)	population-based retrospective cohort study	1 January 2018 – 30 September 2021	Comirnaty or CoronaVac	Inpatients 12 years and older (Hong Kong)	N=38 (myocarditis)	NR	NR	1 or 2 doses	1st dose: IRR=9.15 (95% CI 1.14-73.16); 2nd dose: IRR=29.61 (95% CI 4.04-217.07)	
32	Witberg (71)	Population-based cohort study	42 days after dose 1	Comirnaty	Clalit Health Services, electronic health	n=54 (myocarditis)	94%	Median (IQR) = 27 (21-35) years	1 dose	NC	Overall: 2.13 (95% CI 1.56-

					records for patients aged 16 years or older						2.70) per 100,000
33	Yap (72)	Reports to Singapore's vaccine safety committee	January 2021 – July 2021	mRNA COVID vaccines	Singapore	n=34 (pericarditis, myocarditis, or concomitant pericarditis and myocarditis)	82.40%	Myocarditis median 23 (range 12-55) years	64% followed 2nd dose	NC	NC

NR = Not Reported; NC = Not calculated; SD = Standard Deviation; CI = Confidence Interval; aOR = Adjusted Odds Ratio







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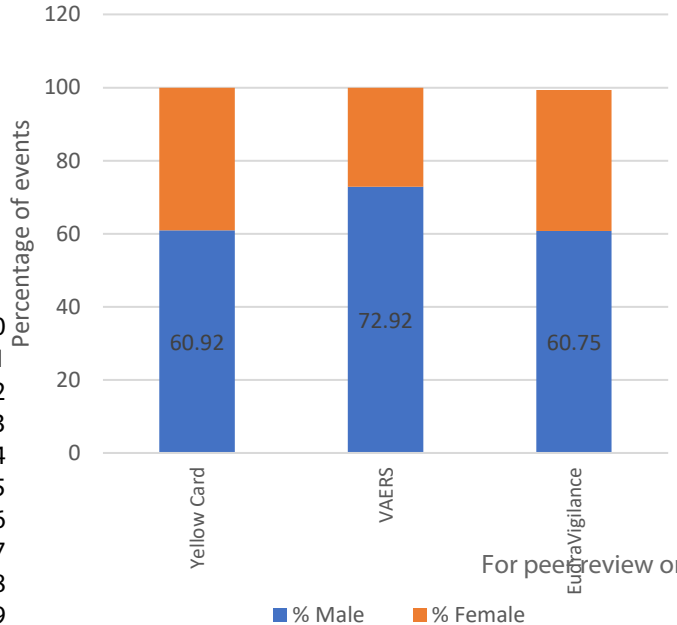

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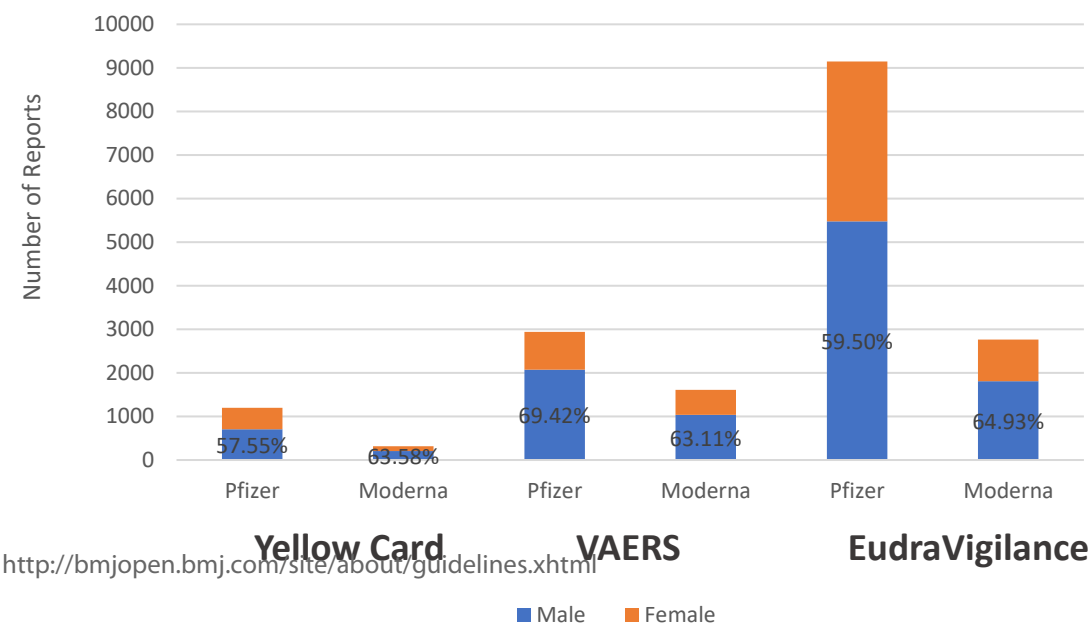

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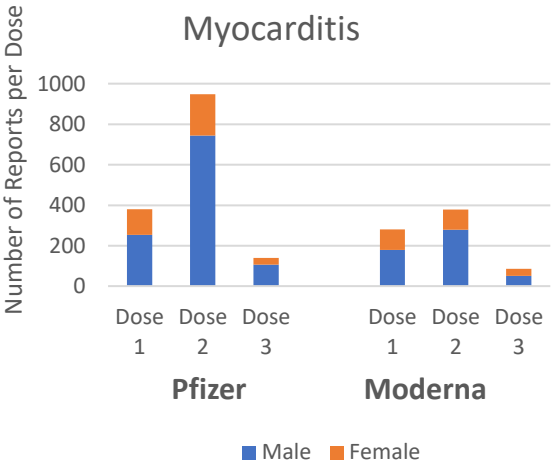

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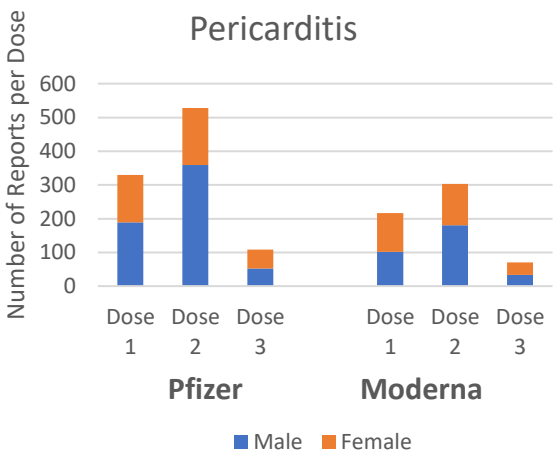

Reporting checklist for cross sectional study.

Based on the STROBE cross sectional guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cross sectionalreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1

Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3 & 4
Objectives	#3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	#4	Present key elements of study design early in the paper	4
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants.	n/a – all patients spontaneously reporting events of myocarditis and pericarditis were included
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and	4 (confounders and effect modifiers not applicable)

		effect modifiers. Give diagnostic criteria, if applicable	
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	4
Bias	#9	Describe any efforts to address potential sources of bias	n/a – not possible to address bias in spontaneously reported data. Biases discussed as a limitation on page 8
Study size	#10	Explain how the study size was arrived at	n/a – all spontaneously reported events of myocarditis and pericarditis to the UK's Yellow Card scheme, US VAERS, and EEA EudraVigilance were included
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	n/a – not applicable in this study

Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	n/a – no statistical methods were applied
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	n/a – not applicable for the data used
Statistical methods	#12c	Explain how missing data were addressed	n/a – not applicable for these datasets; missing information within spontaneous reports mentioned as a limitation on page 8
Statistical methods	#12d	If applicable, describe analytical methods taking account of sampling strategy	n/a – no analytical statistical methods applied; no sampling
Statistical methods	#12e	Describe any sensitivity analyses	n/a – no sensitivity analyses conducted
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	5 & 6; Tables 1, 2, 3a, 3b & 4

Participants	#13b	Give reasons for non-participation at each stage	n/a – all patients reporting myocarditis and pericarditis to spontaneous reporting systems of UK, US and EEA were included up to the datalock point
Participants	#13c	Consider use of a flow diagram	n/a
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	5 & 6; All tables
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	Tables 2-4
Outcome data	#15	Report numbers of outcome events or summary measures. Give information separately for exposed and unexposed groups if applicable.	5 & 6; Tables 1-4
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which	n/a – only descriptive statistics (counts and percentages) used

		confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	Tables 2-4
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a – not appropriate for these data as no comparator
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	5 & 6
Discussion			
Key results	#18	Summarise key results with reference to study objectives	6 & 7
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	7 & 8
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	7 - 9

Generalisability	#21	Discuss the generalisability (external validity) of the study results	9
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2 (see separate checklist for detail)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5/6
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	5/6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	5/6
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5/6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5/6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	N/A (descriptive)
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	6-9
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	N/A
Study characteristics	17	Cite each included study and present its characteristics.	Table 5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	8-9
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	N/A Results presented in Table 5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	N/A
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9-10
	23b	Discuss any limitations of the evidence included in the review.	11
	23c	Discuss any limitations of the review processes used.	11
	23d	Discuss implications of the results for practice, policy, and future research.	11
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	13
Competing interests	26	Declare any competing interests of review authors.	13

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	13-14

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/